VOLUME 62 NUMBER 2

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Archives of Dermatology and Syphilology

VOLUME 62 AUGUST 1950 NUMBER 2

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LESIONS OF THE SCALP IN CERTAIN SCALY DERMATOSES

Histologic Study

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With the Collaboration of Allan A. Dixon, M.D.
MINNEAPOLIS

THE SCALY dermatoses which affect the scalp can be differentiated without difficulty in most instances, especially those which present concomitant lesions on the glabrous skin. In some cases, however, their clinical distinction is not easy, especially if the disease is limited to the scalp. In this study, biopsies were performed in a number of common squamous disorders which may affect the scalp, in an effort to appraise the diagnostic value of the histologic observations. There is a rather surprising paucity of information on the subject in various textbooks, even those which deal specifically with diseases of the hair and scalp.

The material for the study consisted of histologic sections from 8 cases of circumscribed neurodermatitis (suboccipital dermatitis, lichen chronicus simplex), 13 of psoriasis, 14 of seborrheic dermatitis, 15 of chronic discoid lupus erythematosus and 5 of lichen planus. Since emphasis is placed on the histologic observations, clinical features will be mentioned but briefly and only when pertinent to the differential diagnosis.

CIRCUMSCRIBED NEURODERMATITIS (SUBOCCIPITAL DERMATITIS, LICHEN CHRONICUS SIMPLEX)

The histologic observations in sections from patients with dermatitis of the nuchal region showed considerable variation. Hyperkeratosis, although present in most sections, varied a great deal both in degree and regularity. In some cases it was mild but uniform, in others moderate to intense but uniform and in still others mild and spotty. Parakeratosis was present in every section but one, and appeared uniform in some and localized to small areas in others. The stratum granulosum was present in most sections although as a rule it seemed thinner than

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Read as the Presidential address at the annual meeting of the Chicago Dermatological Society, Jan. 18, 1950.

From the Division of Dermatology, University of Minnesota, H. E. Michelson, M.D., director, and the Department of Dermatology, Minneapolis General Hospital, Carl W. Laymon, M.D., director.

normal. Acanthosis was present in all our cases but 1, in which there was a surprising epidermal atrophy. As a rule, the acanthosis was moderate. In some sections it was uniform, although in most of them it was irregular. In most instances the rete pegs were elongated, although no clubbing was noted. Slight to moderate epidermal edema was usually present. We noted no evidence of vesiculation in any of our cases, and no microabscesses were seen. Mitosis in the epidermis was so insignificant that it seemed to be of no diagnostic value. There was nothing noteworthy as far as the basal layer was concerned. In

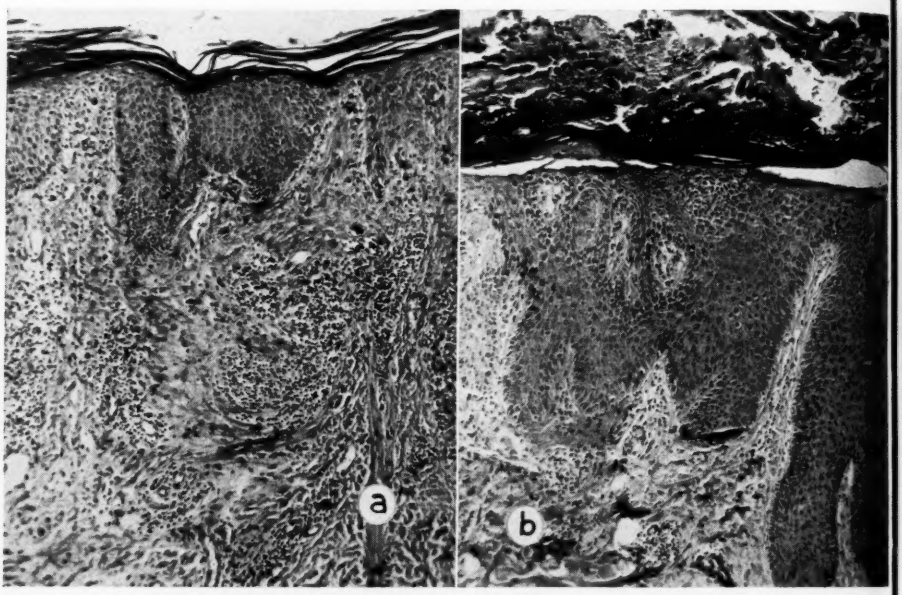

Fig. 1.—(*a*) Neurodermatitis of the suboccipital region, showing parakeratosis simulating psoriasis. Clubbing of the rete pegs is unusual in this disorder. (*b*) Showing accumulation of debris on surface, an infrequent finding in psoriasis of the scalp.

about 25 per cent of the cases crusting was evident, as characterized by accumulation of debris and polymorphonuclear leukocytes on the surface. In all probability this reaction was a result of trauma following scratching.

The features in the cutis were nonspecific. Mild edema was present in most instances along with moderate dilatation of the smaller vessels. The cellular infiltrate was usually located in the upper portion of the cutis about the vessels and ranged from mild to moderate in intensity.

There was no tendency toward arrangement about follicles or glands. The infiltrate was almost exclusively lymphocytic, although occasionally polymorphonuclear leukocytes and eosinophils or red blood cells could be seen.

In 1946 Sachs, Miller and Gray [1] discussed the "neurodermatitic reaction," a term which was used to represent a pathologic process rather than a disease and which applied to such dermatoses as neurodermatitis, nummular eczema and exudative lichenoid and discoid chronic dermatitis. The authors stated:

> The pathologic process involves both the epidermis and the cutis: The former is dry and, although the intercellular spaces may be accentuated, the basal cell margin is unaltered; the granular and horny layers are present and may be increased, and a rather regular acanthosis is usually present. However, friction, scratching, medication, etc., may superimpose a traumatic dermatitis. This would account for the presence of an irregular acanthosis, edema and even parakeratosis.

They felt, also, that the changes in the cutis were nonspecific and concluded that the pathologic observations could not establish a final diagnosis.

Ormsby and Montgomery [2] described similar histologic features and mentioned that the histologic picture of neurodermatitis closely simulates that seen in some cases of psoriasis.

Lynch,[3] in his recent discussion of suboccipital dermatitis, described similar changes and brought out the difficulties in the histologic diagnosis of neurodermatitis, psoriasis and seborrheic dermatitis. He concluded, after a review of the microscopic changes, that histologic examination was of no great aid in differential diagnosis. Our studies confirm his views.

PSORIASIS VULGARIS

Ormsby and Montgomery [2] stated that the histologic diagnosis of psoriasis usually can be made if a well developed papule is selected for biopsy. Our studies indicate that psoriatic lesions of the scalp do not constantly exhibit the histologic changes regarded as characteristic. We found that hyperkeratosis and parakeratosis were present in every case, although there was extreme variation in intensity. In some cases there was practically no hyperkeratosis, while in others it was extreme. Parakeratosis was present in every case, although in about half it was

1. Sachs, W.; Miller, C. S., and Gray, M. B.: Neurodermatitic Reaction, Arch. Dermat. & Syph. **54**:397-407 (Oct.) 1946.

2. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Philadelphia, Lea & Febiger, ed. 7, 1948, p. 360.

3. Lynch, F. W.: Suboccipital Dermatitis, Arch. Dermat. & Syph. **60**:307-317 (Sept.) 1949.

not uniform but spotty and slight. Almost without exception there was a great diminution in the thickness of the stratum granulosum. In some cases it was uniformly absent, while in others it was present only in small, localized areas. Certainly in psoriasis this layer was more conspicuous by its almost complete absence than in circumscribed neurodermatitis. Generally speaking, parakeratosis was present more regularly and extensively in psoriasis than in neurodermatitis, although the difference was not so great as to afford an important differential point. Acanthosis, which ranged from mild to rather intense, was present in

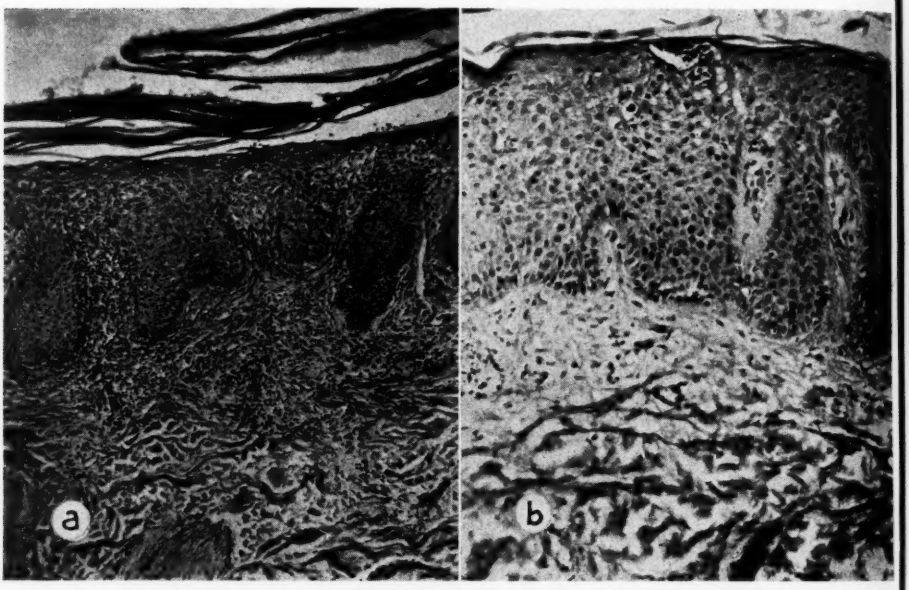

Fig. 2.—(*a*) Psoriasis of the scalp, showing parakeratosis, clubbing of pegs, lack of stratum granulosum and nonspecific infiltrate in cutis. (*b*) Characteristic microabscess in epidermis.

most cases and was more regular than in neurodermatitis. The rete pegs were more uniformly elongated and clubbed than in neurodermatitis. In our opinion, the amount of intercellular edema in the epidermis was less than in neurodermatitis, although this point alone was not an important help in differential diagnosis. The number of mitoses in the epidermis and the presence or absence of pigment seemed to be of no value in differentiating psoriasis from neurodermatitis. Microabscesses were not always found, but in our cases no serial sections were made. Microabscesses, however, were never observed in our cases of neurodermatitis.

Just as in neurodermatitis, the changes in the cutis were nonspecific and nondiagnostic. In some cases no edema was seen, while in others it was present to a mild degree. In practically every case the infiltrate was moderate and for the most part was arranged about the vessels. There was no special localization about the hair follicles or sebaceous glands. In 1 case the infiltrate was intense and diffuse. The cells were mostly lymphocytes, although monocytes and plasma and mast cells were occasionally seen. Eosinophils were rarely found.

We agree with Burks and Montgomery [4] that the histologic differentiation between chronic plaques of psoriasis and plaques of localized neurodermatitis is most difficult. These authors emphasized that both diseases present regular acanthosis and papillomatosis with long and narrow rete ridges and thinning of the suprapapillary plates. In a chronic quiescent psoriatic plaque microabscesses often are absent or few and far between and the infiltrate is composed chiefly of mononuclear cells similar to those seen in localized dermatitis. Burks and Montgomery mentioned that dilatation, tortuosity and apparent rigidity of the walls of the capillaries usually were found in psoriasis and were absent in neurodermatitis. We were unable to note this difference. We believe that the differential diagnosis between the two dermatoses is especially difficult when they occur on the scalp.

SEBORRHEIC DERMATITIS

Our cases of seborrheic dermatitis of the scalp were especially selected. We chose those cases in which there were enough concomitant evidences of seborrheic dermatitis to make the clinical differentiation between that disorder, psoriasis and localized neurodermatitis quite certain but which had patches (usually in the suboccipital region) which might easily be confused clinically with patches of psoriasis or neurodermatitis. Most of these patients presented fairly characteristic lesions in the postauricular, presternal or interscapular regions and axillas or groins. It is generally agreed that distinction between certain types of seborrheic dermatitis and psoriasis is often difficult. It seems to be true that, the more difficult the clinical distinction, the more difficult the histologic differentiation. In our cases of seborrheic dermatitis there was mild to moderate hyperkeratosis, which was irregular rather than uniform in almost every instance. Parakeratosis was notably less intense and constant than in neurodermatitis or psoriasis and was entirely absent in some cases. The stratum granulosum was thick, thin or absent and hence was of no diagnostic value. Epidermal edema was present, though

4. Burks, J. W., and Montgomery, H.: Histopathologic Study of Psoriasis, Arch. Dermat. & Syph. **48**:479-493 (Nov.) 1943.

for the most part not pronounced. The degree of acanthosis was slight to moderate, and no clubbing of the rete pegs was seen.

The observations in the cutis were also nondiagnostic and consisted of dilatation of the superficial vessels and a perivascular infiltrate composed of lymphocytes, polymorphonuclear leukocytes and occasional plasma cells. Here, too, the infiltrate was not arranged about follicles or glands. There were no important differential features between seborrheic dermatitis and either of the aforementioned disorders.

There were 2 cases of acute seborrheic dermatitis in which there was little difficulty in making either a clinical or histologic differentiation

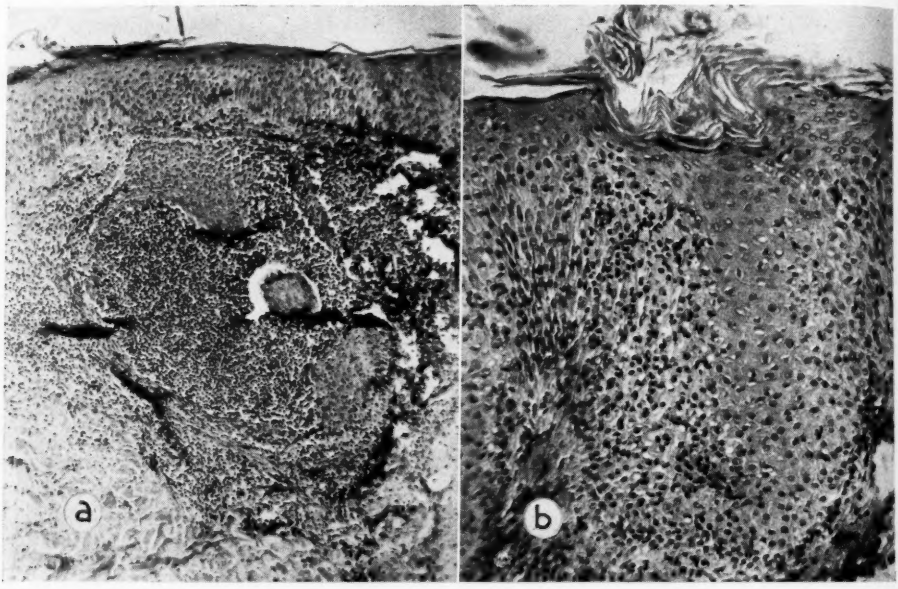

Fig. 3.—(*a*) Seborrheic dermatitis of scalp, showing heavy infiltrate of polymorphonuclear leukocytes with formation of abscess in cutis. (*b*) Showing migration of polymorphonuclear leukocytes through epidermis (microabscess), as seen in psoriasis.

from psoriasis or neurodermatitis. In the sections from them there was much more spongiosis and much more edema in the cutis plus a much more intense and diffuse infiltrate containing many polymorphonuclear leukocytes, even to the point of abscess formation in the papillary portion of the cutis and stratum corneum.

It has been claimed that the presence of droplets of fat in the epidermis, especially in the stratum corneum and the basal cells but also about the superficial blood vessels, occurs in seborrheic dermatitis but

not in other forms of eczema. In this study no special stains for lipids were made. Williams, Montgomery and Powell [5] recently found, however, that stains for fat revealed little, if any, lipid in the stratum corneum and none in the rest of the epidermis in seborrheic dermatitis.

LUPUS ERYTHEMATOSUS

All our cases of lupus erythematosus of the scalp were of the chronic discoid variety. Five of our 15 cases were previously studied by Laymon and Murphy.[6] Michelson [7] brought out the fact that the pathologic changes in this type of lupus erythematosus are made up of three distinct processes: first, a vascular or perivascular disturbance; second, edema and subsequent damage of connective tissue, followed by an infiltration, and, third, epidermal and follicular alterations. He emphasized that the changes depended to some degree on the type of lesion under consideration and that a uniform picture for lupus erythematosus does not exist. Even though the epidermal changes are secondary to the inflammatory process in the cutis, they are of aid in diagnosis, and, since we have described epidermal changes first in the other diseases under consideration, we shall follow the same procedure for lupus erythematosus. In our cases the degree of hyperkeratosis was mild and insignificant in some, moderate in others and extreme in others. Dilatation and plugging of the follicles were present in some cases, but were not constantly observed. The granular layer was preserved in almost every instance and in many cases was thickened. Epidermal atrophy was present in almost all cases, although in a few there were areas where papillomatosis was noted. In most cases the basal outline was almost flat and the basal layer was vacuolated, degenerated and disrupted.

In the cutis, dilatation of the small blood vessels, particularly in the upper portions, was a prominent feature. Edema, which varied from moderate to intense, as a rule was severer than in any of the diseases previously discussed. The infiltrate was present in various amounts and in masses of different shapes. Some of the masses were globular, apparently being separated from each other by practically normal connective tissue. In some sections the infiltration was follicular and perivascular, although at many points it was neither. The lymphocyte was the predominant cell, although a few leukocytes were seen. Plasma, mast and giant cells were conspicuous by their absence. Deeper in the cutis the infiltrate was rather heavily focused about sweat glands. In

5. Williams, H. L.; Montgomery, H., and Powell, W. N.: Dermatitis of Ear, J. A. M. A. **113**:641-646 (Aug. 19) 1939.

6. Laymon, C. W., and Murphy, R. J.: The Cicatricial Alopecias, J. Invest. Dermat. **8**:99-122 (Feb.) 1947.

7. Michelson, H. E.: The Problem of Lupus Erythematosus, California Med. **70**:1-5 (Jan.) 1949.

most cases of lupus erythematosus of the scalp the sebaceous glands and follicles were destroyed early by the inflammatory process. Staining by the Weigert method showed severe disruption of elastic tissue in the papillary portions of the cutis, as manifested by fragmentation and splitting, with complete disappearance in areas of maximum infiltration. The infiltrate in lupus erythematosus was distributed entirely differently in active cases than in other types of cicatricial alopecias such as pseudopelade, being much heavier and more diffuse in the upper part of the edematous cutis in lupus erythematosus.

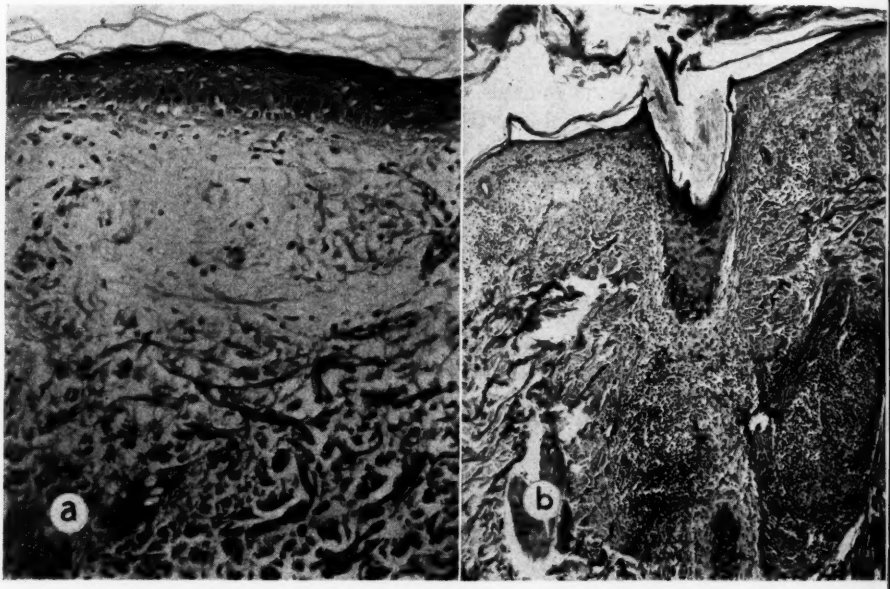

Fig. 4.—(*a*) Chronic discoid lupus erythematosus of scalp, showing extreme edema of cutis. (*b*) Showing epidermal alterations: hyperkeratosis, atrophy and follicular dilatation, with globular masses of infiltrate in the cutis.

Features of sections from old inactive lesions of lupus erythematosus were entirely nondiagnostic. All that could be said was that the picture was the result of some cicatrizing process. The epidermis was extremely atrophic, the rete pegs completely flattened, the entire cutis practically homogenized, the sebaceous glands and follicles gone and the sweat glands so shrunken that they were almost gone. The infiltrate, perhaps the chief feature of the active process, had entirely disappeared.

The presence of concomitant lesions of lupus erythematosus on the glabrous skin usually expedites the diagnosis. Rarely, however, the

disorder may be limited to the scalp and give rise to clinical diagnostic confusion. In these instances histologic examination is usually distinctly helpful.

LICHEN PLANUS

Lichen planus of the scalp usually presents features which are identical with those characterizing lichen planus on the other parts of the body. Relative and absolute hyperkeratosis, increase in the stratum granulosum, acanthosis and liquefaction degeneration of the basal layer constitute the

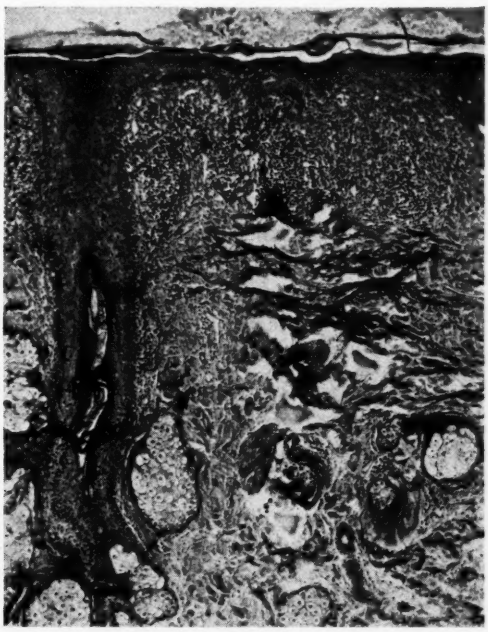

Fig. 5.—Lichen planus of the scalp, showing hyperkeratosis, granulosis, degeneration of the basal layer and a sharply marginated infiltrate in the upper part of the cutis.

important changes which affect the epidermis. Parakeratosis was not noted in our cases. In the cutis changes in the blood vessel are not a striking feature. In the scalp, just as in other areas of the body, the sharply marginated infiltrate composed chiefly of lymphocytes with occasional polymorphonuclear leukocytes constitutes an important observation. This is not invariably present, however, as was exemplified in 1 of our cases in which there were characteristic papules of lichen planus on the scalp. Histologic examination showed only a spotty infiltrate in

the upper portions of the cutis. We noted that in our cases there was a sharp band of infiltrate hugging the follicle as well as the diffuse sharply marginated infiltrate between the follicles.

Lichen planus is rarely limited to the scalp, and in cases in which there are concomitant lesions on the glabrous skin there is no difficulty in differentiating the lesions on the scalp from patches of neurodermatitis, psoriasis, seborrheic eczema or lupus erythematosus. We observed 1 patient, however, who had extensive lichen planus with plaques in the nuchal region. If the latter had been observed alone it would have been most difficult to differentiate them clinically from patches of circumscribed neurodermatitis. In this instance, however, the histologic observations were characteristic for lichen planus.

SUMMARY

In this study biopsies were performed in 8 cases of circumscribed neurodermatitis (suboccipital dermatitis, lichen chronicus simplex), 13 of psoriasis, 14 of seborrheic dermatitis, 15 of chronic discoid lupus erythematosus and 5 of lichen planus involving the scalp in an effort to appraise the value of the histologic observations from the diagnostic standpoint.

Neurodermatitis also presents varying degrees of hyperkeratosis and parakeratosis, although the latter is not as regular and uniform as in psoriasis. The acanthosis is not as regular, nor is there the tendency to clubbing seen in psoriasis. Epidermal edema seems to be more noticeable in neurodermatitis. The changes in the cutis do not afford any exceptional point of differentiation. No microabscesses were found in our cases of neurodermatitis.

Psoriasis presents a combination of changes, consisting of uniform to spotted or layered parakeratosis, diminution or absence of the stratum granulosum, regular acanthosis, mild epidermal edema, uniform and regular papillomatosis with clubbing of the papillary bodies and mild perivascular infiltration of lymphocytes and monocytes in the upper portion of the cutis, with migration of polymorphonuclear leukocytes through the epidermis resulting in the formation of microabscesses. In most cases, however, all these features were not present in any one section.

The changes in seborrheic eczema depend on the clinical acuity of the process. There is a greater tendency to spongiosis, and the infiltrate in the cutis is likely to be more intense and diffuse and contains more polymorphonuclear leukocytes.

The combination of changes in lupus erythematosus, beginning with vascular dilatation in the upper portions of the cutis followed by edema and varying amounts of infiltrate plus secondary epidermal changes consisting of hyperkeratosis, keratotic plugging, atrophy and degener-

ation of the basal layer afford, as a rule, a characteristic picture. Our studies indicate that the histologic features in discoid lesions of the scalp are most suggestive but not pathognomonic in all cases. The features of sections from old inactive lesions which were examined were entirely nondiagnostic.

The histologic features of lichen planus of the scalp are about the same as those of lesions of the disease found elsewhere on the body. Hyperkeratosis, granulosis, acanthosis, degeneration of the basal cell layer and the sharply marginated infiltrate in the upper part of the cutis are characteristic and usually present. In lesions of the scalp the infiltrate tends to hug the follicle more than in lesions elsewhere on the body.

CONCLUSIONS

Histologic examination of lesions of the scalp in circumscribed neurodermatitis, psoriasis and seborrheic dermatitis does not permit a positive diagnosis in most cases.

In contrast, lupus erythematosus and lichen planus present a diagnostic microscopic picture in the majority of instances.

Medical Arts Building.

COMPARISON OF MUSCLE BIOPSIES AND BONE MARROW EXAMINATIONS IN DERMATOMYOSITIS AND LUPUS ERYTHEMATOSUS

JOHN F. MADDEN, M.D.
With the Collaboration of Irvine M. Karon, M.D.
ST. PAUL

THE DIFFICULTY encountered in differentiating acute disseminated lupus erythematosus from dermatomyositis prompted us to evaluate muscle biopsies on a series of patients with these diseases, and, because Hargraves found a heretofore undescribed cell in bone marrow preparations from patients with acute disseminated lupus erythematosus, we added a search for such cells to our investigations. The following communication is an effort to compare and correlate the observations made during such searches on 27 patients, 8 of whom had dermatomyositis and 19 of whom had lupus erythematosus (11, acute disseminated; 7, subacute, and 1, chronic).

There are a large number of diseases which are similar and often confused with the two diseases under discussion. The list is long and emphasizes why any positive aids in diagnosis should be carefully appraised. Poikiloderma atrophicans vasculare,[1] diffuse scleroderma,[2] scleredema adultorum,[3] trichinosis, polyarteritis nodosa, glomerulo-

Read at the Sixty-Ninth Annual Meeting of the American Dermatological Association, Inc., at Hot Springs, Va., May 28, 1949.

From the Department of Dermatology and Syphilology, Ancker Hospital, St. Paul, Dr. John F. Madden, director, and the Division of Dermatology and Syphilology, University of Minnesota, Dr. H. E. Michelson, director.

1. (*a*) Dowling, G. B., and Griffiths, W. J.: Dermatomyositis and Progressive Scleroderma, Lancet **1**:1424-1428 (June 24) 1939. (*b*) O'Leary, P. A., and Waisman, M.: Dermatomyositis: Study of 40 Cases, Arch. Dermat. & Syph. **41**:1001-1019 (June) 1940.

2. (*a*) Dowling and Griffiths.[1a] (*b*) Talbott, J. H.; Gall, E. A.; Consolazio, W. V., and Coombs, F. S.: Dermatomyositis with Scleroderma Calcinosis and Renal Endarteritis Associated with Focal Cortical Necrosis: Report of Case in Which Condition Simulated Addison's Disease, with Comment on Metabolic and Pathologic Studies, Arch. Int. Med. **63**:476-496 (March) 1939. (*c*) O'Leary, P. A.: Dermatosclerosis, Canad. M. A. J. **48**:410-415 (May) 1943. (*d*) Klemperer, P.; Pollack, A. D., and Baehr, G.: Diffuse Collagen Disease: Acute Disseminated Lupus Erythematosus and Diffuse Scleroderma, J. A. M. A. **119**:331-332 (May 23) 1942.

3. O'Leary.[2c] Klemperer, Pollack and Baehr.[2d]

nephritis,[4] myasthenia gravis,[5] pellagra,[6] adrenal disease,[5] sclerema neonatorum, rheumatic fever,[7] polyneuritis,[5] acrosclerosis,[2c] erythema multiforme,[8] sunlight dermatitis,[4] toxic erythema,[4] erysipelas,[9] arthralgias and arthritis,[4] cardiac disease,[4] subacute bacterial endocarditis,[7c] panniculitis,[5] purulent embolic myositis,[5] postinfectious asthenias[5] and functional states of exhaustion[5] as well as other diseases and syndromes may be included in a differential diagnosis, but our concern here is confined to dermatomyositis and lupus erythematosus.

Objections might be voiced about the titles of dermatomyositis and lupus erythematosus, but until the causes and pathogenesis are known no more indicative titles are useful. O'Leary and Waisman [1b] suggested polymyositis as a more accurate descriptive term than dermatomyositis for that syndrome. The term visceral lupus erythematosus has appeared recently in the French literature and is applied to acute cases which have little or no cutaneous involvement. The term is preferable to "lupus erythematosus sine lupus erythematosus." Rothman and Filsher [7c] urged that erythematodes, a term which has long been in common use in European clinics, be substituted for erythematosus. Ever since the disease was first described there have been a great many synonyms used. We shall adhere to the terms lupus erythematosus and dermatomyositis with various adjectives which either are descriptive or designate stages of the processes.

The patients in this study were classified as having chronic, subacute or acute lupus erythematosus. Chronic discoid lupus erythematosus develops gradually from a small lesion to its characteristic appearance by peripheral extension of its border while the center of the lesion becomes atrophic or scarred, or in some instances the lesions do not progress but disappear without leaving a trace. The course is chronic and the general health apparently undisturbed. Acute disseminated lupus erythematosus is a severe, usually fatal systemic disease with or without changes in the skin and may or may not be preceded by the other forms of lupus erythematosus. Subacute lupus erythematosus lies

4. Montgomery, H.: Disseminate Lupus Erythematosus as a Systemic Disease, to be published.

5. O'Leary, P. A.: Pellagra: A Study of 34 Cases in Localities Where Pellagra Is Not Endemic, Northwest Med. **27**:319-323 (July) 1928.

6. (*a*) O'Leary.[5] (*b*) Keefer, C. S., and Felty, A. R.: Acute Disseminated Lupus Erythematosus: Report of 3 Fatal Cases, Bull. Johns Hopkins Hosp. **35**:294-304 (Sept.) 1924.

7. (*a*) Klemperer, Pollack and Baehr.[2d] (*b*) O'Leary.[5] (c) Rothman, S., and Felsher, Z.: Symposium on Advances in Clinical Medicine: Subacute and Acute Disseminated Lupus Erythematodes, M. Clin. North America **31**:198-212 (Jan.) 1947.

8. Montgomery.[4] Keefer and Felty.[6b]

9. Montgomery.[4] O'Leary.[5] Keefer and Felty.[6b]

between the two extremes and may be near the one or the other but never fits clearly into either group. One type may change to the other, and a single patient may experience acute, subacute and chronic phases. The term dermatomyositis was used to cover that disease manifestation for all the patients studied, and that disease is looked on by us as always being systemic.

We studied 8 cases of dermatomyositis, 5 in male and 3 in female patients. The ages ranged from 4 to 49 years. Of the 8 patients all but 1 were alive at the time of writing. There were 11 patients with acute disseminated lupus erythematosus, 7 whose disease was diagnosed as subacute and only 1 patient with chronic discoid lupus erythematosus. The total number of patients with lupus erythematosus investigated was 19. Twelve were female and 7 were male, and the ages ranged from 19 to 67 years. Sixteen of the 19 were between 25 and 55 years of age. Twelve of the patients with lupus erythematosus were alive, and the 7 deaths occurred in those with the acute variety of the disease.

MUSCLE BIOPSIES

Muscle tissue was excised from those muscles most often involved, and we urge future investigators to make their excision from the same muscle in every patient if possible. The pectoralis major and the deltoid muscle are favorable sites. Nine of our specimens were from the pectoral muscle and 6 from the deltoid muscle, while 17 were from various sites. Although biopsies were preferred, Clawson [10] advised us that postmortem specimens if taken within eight hours after death are entirely satisfactory unless, for some reason, the body had become decomposed.

Clawson, Noble and Lufkin [11] stated that the muscle changes in inflammatory diseases such as those mentioned may be divided into the categories of nodular myositis and degenerative processes which consist of atrophy, sarcoplasmic changes (Zenker's degeneration and necrosis) and nuclear changes. The inflammatory nodules consisted primarily of infiltrating lymphocytes, polymorphonuclear leukocytes and plasma cells. The size and number of the inflammatory nodules varied in different patients and at different stages of their disease. Atrophy appeared as shrinking and slight narrowing of the muscle fibers but never progressed to their complete disappearance. The sarcoplasm was lysed and had completely disappeared in the severe examples. Where the sarcoplasmic changes were less marked the fibers were swollen,

10. Clawson, B. J.: Personal communication to the authors.

11. Clawson, B. J.; Noble, J. F., and Lufkin, N. H.: Nodular Inflammatory and Degenerative Lesions of Muscles from 450 Autopsies, Arch. Path. **43**:579-589 (June) 1947.

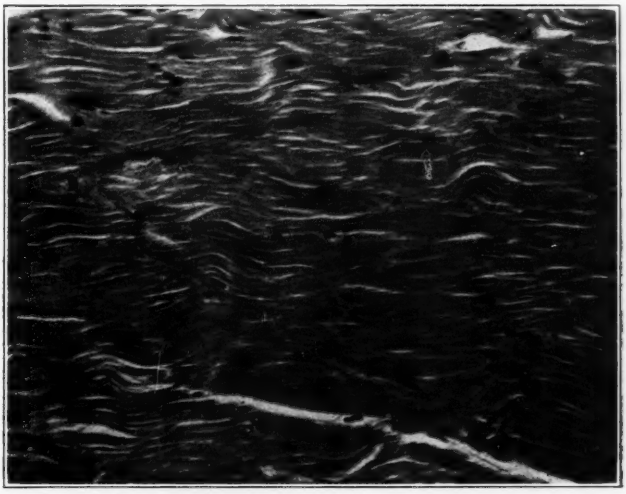

Fig. 1.—Normal muscle.

Fig. 2.—Nodular myositis, showing the collection of polymorphonuclear leukocytes, lymphocytes and plasma cells in one nodule and distributed between the muscle fibers.

stained poorly and in some instances lost both cross and longitudinal striations. Nuclear changes were in size and shape and toward an increase in number, and some nuclei were hyperchromatic.

All twelve biopsy specimens from 8 patients with dermatomyositis showed varying degrees of nodular myositis. The myositis was severer in the acute cases and decreased in intensity as the disease became more chronic.

Nodular myositis was seen in only six of twenty-one specimens from patients with lupus erythematosus. The myositis was severe in only 1 patient, who also had rheumatic fever, and mild in the other persons,

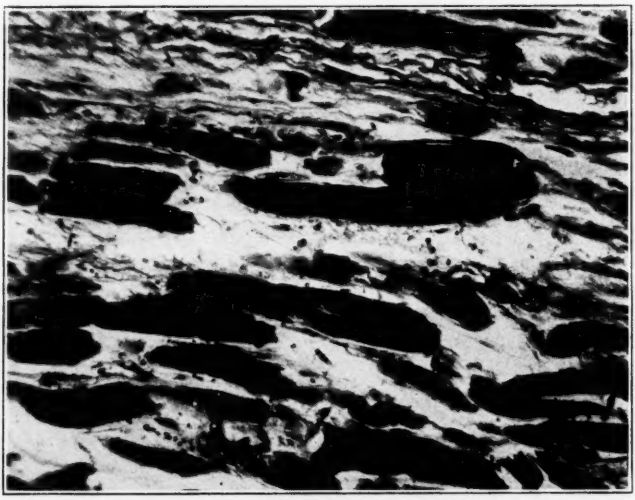

Fig. 3.—Sarcoplasmic changes, showing swollen, poorly stained muscle fibers. The sarcoplasm is lysed and completely absent in some portions.

who had arthralgia, rheumatic pains or rheumatoid arthritis. Nodular myositis was not seen in a single specimen from a patient with lupus erythematosus who did not have rheumatic fever, arthralgia, rheumatic pains or arthritis, regardless of the acuity of the lupus erythematosus. Nodular myositis was not seen in chronic or subacute lupus erythematosus. Three of the 5 patients with acute disseminated lupus erythematosus who showed nodular myositis were alive at the time of writing.

Degenerative processes appeared in all except 1 case of dermatomyositis. The patient was well on the road to recovery when the biopsy specimen was taken. Degenerative processes were seen in only 6 of 19 cases of lupus erythematosus. These changes were very slight except

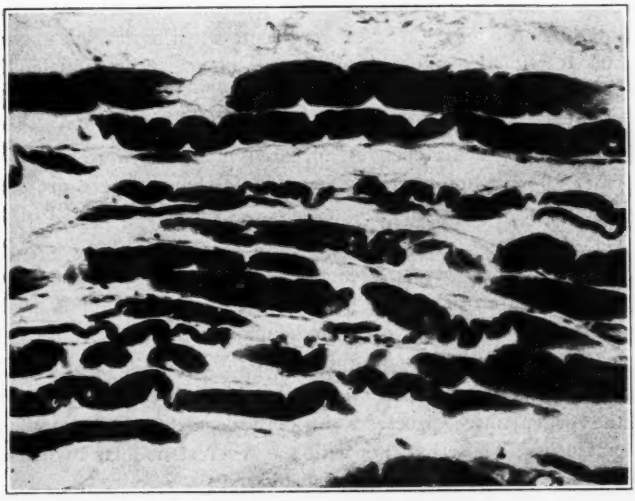

Fig. 4.—Atrophic changes, showing shrinking and narrowing of the muscle fibers.

Fig. 5.—Nuclear changes, showing variations in size and shape, increase in number and hyperchromatic muscle nuclei.

in the patient who had rheumatic fever. Atrophy was mild in three and absent in five biopsy specimens from patients with dermatomyositis, probably because 7 of the 8 cases were acute when the muscle specimens were taken. It was seen in only 1 case of acute disseminated lupus erythematosus and was slight in all specimens taken from persons with dermatomyositis and lupus erythematosus.

Severe sarcoplasmic changes appeared in 5 and were absent in 3 of 8 cases of dermatomyositis. Sarcoplasmic changes were present but insignificant in 4 acute and 2 subacute cases of the total 19 of lupus erythematosus.

Nuclear changes were present in 4 of 8 cases of dermatomyositis and in only 1 case of the acute form of the 19 cases of lupus erythematosus. In both dermatomyositis and lupus erythematosus the nuclear changes were moderate or insignificant.

There appeared to be a definite relationship between nodular myositis and the degenerative processes in both dermatomyositis and lupus erythematosus. Those patients with the severest nodular myositis also showed the greatest degenerative changes.

The muscle changes in dermatomyositis and lupus erythematosus are nonspecific. Similar changes occurred in muscles in idiopathic rheumatoid arthritis,[12] rheumatic fever,[13] diffuse scleroderma,[14] myotonia dystrophia,[12b] pneumonia,[15] thyrotoxicosis[16] and a variety of other disorders. Muscle changes occurred in all our patients with dermatomyositis and in only those persons with acute or subacute lupus erythematosus who had rheumatic fever, arthralgia, arthritis and rheumatoid or muscle pain. It is therefore apparent that microscopic muscle changes are found almost exclusively in those patients who have rheumatic symptoms. In acute disseminated lupus erythematosus the changes were most marked in the patient with rheumatic fever.

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12. (*a*) Desmaris, M. H. L.; Gibson, H. J., and Kersley, G. D.: Muscle Histology in Rheumatic and Control Cases: A Study of 119 Biopsy Specimens, Ann. Rheumat. Dis. **7**:132-142 (Sept.) 1948. (*b*) Jager, B. V., and Grossman, L. A.: Dermatomyositis, Arch. Int. Med. **73**:271-285 (April) 1944.

13. Clawson, Noble and Lufkin.[11] Jager and Grossman.[12b]

14. Brock, W. G.: Dermatomyositis and Diffuse Scleroderma: Differential Diagnosis and Reports of Cases, Arch. Dermat. & Syph. **30**:227-240 (Aug.) 1934.

15. Forbus, W. D.: Pathologic Changes in Voluntary Muscle: I. Degeneration and Regeneration of the Rectus Abdominis in Pneumonia, Arch. Path. & Lab. Med. **2**:318-339 (Sept.) 1926.

16. Dudgeon, L. S., and Urquhart, A. L.: Lymphorrhages in Muscles in Exophthalmic Goitre, Brain **49**:182-186 (June) 1926. Freudenthal, W.: Generalized Scleroderma and Dermatomyositis: Histological Comparison, Brit. J. Dermat. **52**:289-295 (Oct.) 1940.

BONE MARROW EXAMINATIONS

Twenty-one bone marrow examinations were made on 5 patients with dermatomyositis and 16 patients with lupus erythematosus (8 with the acute and 8 with the subacute form). Sundberg [17] stated that bone marrow examinations made at autopsy should not be relied on. Sternal bone marrow specimens from living patients were examined only for Hargraves' L. E. cells with Wright's stain.

Hargraves, Richmond and Morton [18] described a phenomenon which they had observed in bone marrow preparations since 1946. Hargraves named one type of cell an L. E. cell because of its frequent appearance in the bone marrow in cases of acute disseminated lupus erythematosus. Hargraves demonstrated L. E. cells by centrifuging the bone marrow specimen with heparin or sodium oxalate and making the smear from the buffy coat layer of the material. Brunsting [19] stated that Hargraves' recent work indicates that the plasma of patients with acute disseminated lupus erythematosus presents the capacity to produce changes in certain neutrophilic polymorphonuclear leukocytes of the bone marrow and the peripheral blood to bring about the characteristics generally known as the L. E. cell. Haserick and Bortz [20] discovered that plasma from patients with acute disseminated lupus erythematosus contains a substance which regularly induces the L. E. cell and clumping of leukocytes in normal marrow. The L. E. cell practically always involves a mature neutrophilic polymorphonuclear leukocyte. Hargraves stated that chromatin material is found within a large phagocytic vacuole and all gradations of digestion of this material have been observed. Most L. E. cells show a characteristic homogenous, purple-staining mass in the vacuole, but there are instances in which the chromatin pattern is still visible. According to Hargraves, preparations stained with Feulgen's stain show that the material in the vacuoles reacts as nuclear material would. Haserick and Sundberg [21] corroborated Hargraves' work. Sundberg and Lick [22] and Hargraves [23] recently demonstrated L. E. cells in

17. Sundberg, R. D.: Personal communication to the authors.

18. Hargraves, M. M.; Richmond, H., and Morton, R.: Presentation of 2 Bone Marrow Elements: The "Tart" Cell and the "L. E." Cell, Proc. Staff Meet., Mayo Clin. **23**:25-28 (Jan. 21) 1948.

19. Brunsting, L. A.: Personal communication to the authors.

20. Haserick, J. R., and Bortz, D. W.: A New Diagnostic Test for Acute Disseminated Lupus Erythematosus, to be published; Normal Bone Marrow Inclusion Phenomena Induced by Lupus Erythematosus Plasma, to be published.

21. Haserick, J. R., and Sundberg, R. D.: The Bone Marrow as a Diagnostic Aid in Acute Disseminated Lupus Erythematosus: Report on the Hargraves' "L. E." Cell, J. Invest. Dermat. **11**:209-213 (Sept.) 1948.

22. Sundberg, R. D., and Lick, N. B.: "L. E." Cells in the Blood in Acute Disseminated Lupus Erythematosus, J. Invest. Dermat. **12**:83-84 (Feb.) 1949.

23. Hargraves, M. M.: Personal communication to H. Montgomery.

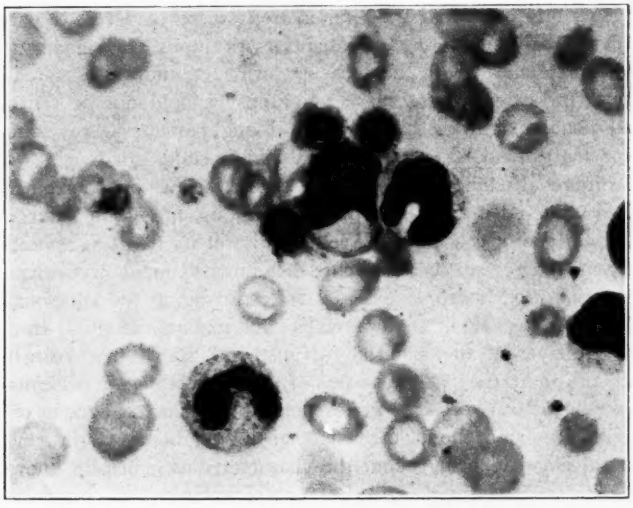

Fig. 6.—Normal sternal bone marrow preparation stained with Wright's stain.

Fig. 7.—Bone marrow preparation showing one L. E. cell surrounded by three polymorphonuclear leukocytes and one lymphocyte.

the peripheral circulating venous blood in patients with acute disseminated lupus erythematosus.

L. E. cells were not found in 6 patients with subacute lupus erythematosus nor in 5 patients with dermatomyositis. All observers have expressed agreement that the L. E. cells decrease in number as the acuity of lupus erythematosus subsides. In other words, L. E. cells are the most numerous in the early, acute phase of acute disseminated lupus erythematosus when it may be the most difficult to establish a diagnosis. As far as we know, L. E. cells have been found only in acute disseminated lupus erythematosus except in 2 instances: in 1 patient with multiple myeloma and in 1 patient with cirrhosis of the liver.[24]

L. E. cells are not always present in acute disseminated lupus erythematosus. They were found in 7 of 11 of Morton's [25] patients, in 4 of 5 of Haserick and Sundberg's [21] patients, in 5 of 7 of Montgomery and McCreight's [26] patients, and in 4 of 8 of our patients with acute disseminated lupus erythematosus whose bone marrows were examined. The finding of L. E. cells in our group of patients with acute disseminated lupus erythematosus had definite prognostic as well as diagnostic significance. The 4 patients who showed L. E. cells in the bone marrow were alive at the time of writing, while the 4 whose bone marrow did not show L. E. cells were dead. This observation may seem contrary to the findings of Montgomery,[4] Brunsting [27] and others of the Mayo Clinic group who have expressed the belief that the presence of L. E. cells is a poor prognostic sign. Taken by and large, the presence of L. E. cells is a poor prognostic sign because they are found almost always in acute disseminated lupus erythematosus, which in itself has a poor prognosis. However, the fact remains that our 4 patients with acute disseminated lupus erythematosus who showed L. E. cells in the bone marrow were still alive at the time of writing while the 4 patients with acute disseminated lupus erythematosus in whom we did not find L. E. cells had died.

It is clearly noted from the aforementioned observations that the L. E. cell occurs often enough in acute disseminated lupus erythematosus to be of diagnostic value. It is particularly valuable in differential diagnosis between dermatomyositis and lupus erythematosus and in those rare cases of visceral lupus erythematosus without cutaneous manifestations.

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24. Hargraves, M. M.: Personal communication to the authors.

25. Morton, R. J.: A Study of the Blood and Bone Marrow in Cases of Disseminated Lupus Erythematosus, Thesis, University of Minnesota, February 1947.

26. Montgomery, H., and McCreight, W. G.: Disseminate Lupus Erythematosus, Arch. Dermat. & Syph. **60**:356-372 (Sept.) 1949.

27. Brunsting, L. A.: Personal communication to the authors.

SUMMARY

A total of 27 patients, 8 of whom had dermatomyositis and 19, lupus erythematosus (11 the acute disseminated, 7 the subacute and 1 the chronic form), were studied.

Thirty-three muscle biopsies were performed in 8 cases of dermatomyositis, 11 cases of acute disseminated lupus erythematosus, 6 cases of subacute lupus erythematosus and 1 case of chronic discoid lupus erythematosus.

All 12 biopsies on 8 patients with dermatomyositis showed varying degrees of nodular myositis. The myositis was severer in the acute cases and decreased in intensity as the disease became chronic.

Nodular myositis was seen in only 6 of 21 biopsy specimens from patients with lupus erythematosus. The myositis was severe in only 1 patient, who also had rheumatic fever, and mild in the other patients, who also had arthralgia, rheumatic pains or rheumatoid arthritis. Nodular myositis was not seen in a single case of lupus erythematosus that was not associated with rheumatic fever, arthralgia, rheumatic pains or arthritis, regardless of the acuity of the lupus erythematosus. Nodular myositis was not seen in chronic or subacute lupus erythematosus.

Degenerative processes in muscles appeared in all except 1 patient with dermatomyositis. Degenerative processes in muscles were seen in only 6 of 19 cases of lupus erythematosus. These changes were very slight except in the patient who also had rheumatic fever. Degenerative processes in muscles by themselves are of little assistance in making a diagnosis.

The presence of nodular myositis, with or without degenerative muscle changes, is in favor of the diagnosis of dermatomyositis over acute disseminated lupus erythematosus unless acute disseminated lupus erythematosus is associated with rheumatic fever, arthralgia, rheumatic pains or arthritis. In these instances muscle biopsies are of little or no value. There may be other confused or associated diseases mentioned early in this report in which muscle biopsies would not be a helpful differential aid. The muscle changes in dermatomyositis and lupus erythematosus are nonspecific.

Twenty-one sternal bone marrow examinations with special reference to L. E. cells were made in 5 cases of dermatomyositis, 8 cases of acute disseminated lupus erythematosus and 6 cases of subacute lupus erythematosus.

L. E. cells were not found in the bone marrow from cases of dermatomyositis or subacute or chronic lupus erythematosus, and they were found in only half the cases of acute disseminated lupus erythematosus.

The number of L. E. cells decreased as the systemic symptoms subsided. L. E. cells are most numerous in the early, acute phase of acute

disseminated lupus erythematosus and therefore are of most diagnostic value when it may be most difficult to establish a diagnosis.

L. E. cells were seen in the 4 patients with acute disseminated lupus erythematosus who survived but were not found in 4 who died. The finding of L. E. cells in our group with acute disseminated lupus erythematosus had definite prognostic as well as diagnostic significance. Taken by and large, the presence of L. E. cells is obviously a poor prognostic sign because they are found almost always in acute disseminated lupus erythematosus, which in itself has a poor prognosis. However, the fact remains that our patients with acute disseminated lupus erythematosus who showed L. E. cells in the bone marrow lived while those who did not show these cells died.

L. E. cells are a valuable diagnostic aid, especially in those cases of acute disseminated lupus erythematosus without cutaneous manifestations.

Bone marrow examinations and muscle biopsies should be an aid in making the differentiation between dermatomyositis and lupus erythematosus.

The biopsy specimens of muscle were studied by B. J. Clawson, M.D., Professor of Pathology, University of Minnesota.

The bone marrow specimens were studied by R. Dorothy Sundberg, Ph.D., Assistant Professor of Anatomy and Hematologist at the University Hospitals, University of Minnesota.

ABSTRACT OF DISCUSSION

Dr. Earl W. Netherton, Cleveland: Drs. Madden and Karon have emphasized that dermatomyositis and acute disseminated lupus erythematosus are serious, complex, systemic diseases and that their differentiation may be difficult, requiring thorough investigation as well as the consideration of a variety of diseases and syndromes. Their study was prompted by the need of diagnostic aids.

They found pathologic changes in the muscles of all their patients with dermatomyositis; however, muscle changes were observed in but 33 per cent of their patients with acute lupus erythematosus and only in patients who had arthritis, arthralgia and rheumatoid or muscle pains. Muscle changes were nonspecific and identical in both diseases with those sometimes observed in a number of other diseases. Consequently, such observations can be evaluated only when correlated with clinical and laboratory data in each particular case.

My associates and I found that muscle tissue obtained in 5 cases of acute lupus erythematosus revealed little of diagnostic significance; furthermore, I doubt whether the minor surgical procedure of obtaining these specimens should be carried out routinely in acutely ill patients. Recently we observed pronounced exacerbation of systemic and cutaneous manifestations in 2 cases of acute disseminated lupus erythematosus within twelve hours after the trauma involved in the taking of a muscle specimen for biopsy.

Recognition of the L. E. cell by Hargraves, Richmond and Morton was an important discovery. Accumulated observations seem to indicate that finding the L. E. cell in the bone marrow or peripheral blood is a diagnostic aid of major importance and may be considered a criterion for the diagnosis of acute dissemi-

nated lupus erythematosus. It is of special value in the identification of acute lupus erythematosus without cutaneous lesions. For reasons unknown the L. E. cell has not been found in the bone marrow preparations of patients with chronic or subacute lupus erythematosus.

During the past six months my interest in the L. E. cell has been increased by the work of my associate, Dr. John Haserick, in collaboration with Dr. Donald Bortz, hematologist at the Cleveland Clinic. They discovered that the L. E. cell was produced in heparinized normal bone marrow after the addition of blood plasma from patients with acute and subacute lupus erythematosus. This observation enhances the value of the L. E. cell as a diagnostic aid. A report of this work has been submitted for publication. Recently, Hargraves reported identical observations and suggested that the L. E. cell phenomenon is probably of immunologic nature.

Haserick and Bortz have studied a series of 10 cases of acute lupus erythematosus. The plasma of all the patients produced the L. E. cell in normal bone marrow preparations. Studies of bone marrow were made in 8 cases. The L. E. cell was found in the marrow in only 4 of the 8 patients. However, the plasma from all 8 patients produced the cell in normal bone marrow preparations. The L. E. cell was found in the marrow of acutely ill patients but not in patients who were having partial remission of their disease or whose cases should probably have been classified as severe subacute or borderline ones.

Plasma from 9 patients produced the L. E. phenomenon in thirty-six normal marrow preparations. Plasma from 1 patient produced the L. E. cell in twenty-seven consecutive normal bone marrow preparations.

Five of the 10 patients had no eruption when their plasma was obtained. Three of the 5 had typical cutaneous manifestations later.

Plasma of patients with chronic discoid lupus erythematosus, scleroderma, rheumatoid arthritis, cirrhosis of the liver and dermatomyositis (1 case) and that from several normal persons failed to produce the L. E. phenomenon.

In 3 cases of acute lupus erythematosus studied by Haserick and Bortz the plasma was fractionated and the various fractions were added to normal bone marrow preparations. So far, these investigators have found that the gamma globulin is the only fraction which causes the formation of the L. E. cell. Plasma from chronic discoid lupus erythematosus in which there was an increase in the gamma globulin did not produce the phenomenon.

I doubt that the presence of the L. E. cell can be considered a favorable prognostic sign in acute lupus erythematosus. However, I am in full agreement with the other observations and views of Drs. Madden and Karon. Their excellent paper is timely and should stimulate interest in and further investigation of the L. E. cell phenomenon.

I believe the technic of Haserick and Bortz and Hargraves provides a test of diagnostic value in the differential diagnosis of acute and subacute disseminated lupus erythematosus. Further study of this phenomenon is needed before its ultimate value can be determined.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: It is obvious that lupus erythematosus is a systemic disease, even in the chronic discoid phase. The present system of classification of the various stages of the disease is artificial, although we use the term "disseminated lupus erythematosus" when there are immunologic phenomena of overreaction. It is not often that disseminated lupus erythematosus is confused with dermatomyositis. Montgomery expressed the opinion that in disseminated lupus the inflammatory and degenerative changes in the muscle are secondary to the involvement of the interseptal vessels. In dermatomyositis, the degenerative changes in the muscle are out of proportion to the degree of inflam-

mation. The Hargraves phenomenon is manifested by peculiar changes which appear in certain neutrophil leukocytes in the bone marrow or peripheral blood when they are brought into contact with the serum of patients who have disseminated lupus erythematosus. The essential features include chemotaxis, nucleolysis and phagocytosis. The phenomenon is probably an immune reaction; it can be demonstrated especially in the bone marrow of most but not all patients who have systemic lupus erythematosus; it is not necessarily of prognostic significance. It is particularly valuable in the diagnosis of so-called lupus erythematosus sine lupus erythematosus, where the cutaneous manifestations are minimal or absent.

Dr. J. Lamar Callaway, Durham, N. C.: It has been a pleasure to listen to this paper. The degenerative changes described as Zenker's necrosis are, as stated, nonspecific and occurred in their series only in patients with rheumatic symptoms.

The Hargraves L. E. cell has interested me a great deal; however, I have never been able to identify it in smears from bone marrow of my patients with acute disseminated lupus erythematosus. Prolonged exposure of blood or bone marrow leukocytes to anticoagulants may produce artefacts which may make the identification of cells difficult, if not impossible. In my experience, smears made from buffy coats are of little value. As Dr. Madden has pointed out, it is difficult to explain why the Hargraves L. E. cell was found in the bone marrow of his patients with acute disseminated lupus erythematosus who lived and was not found in those patients who died. If this cell carries the unfavorable prognosis generally attributed to it I would have expected it to be present in the marrow of patients whose cases had a fatal termination.

In view of Dr. Hargrave's recent paper in the *Proceedings of the Staff Meetings of the Mayo Clinic,* it appears that the L. E. cell can be produced in vitro with the use of normal bone marrow elements on the addition of blood plasma from a patient with acute disseminated lupus erythematosus. This phenomenon appears to be a result of an immunologic response. The test, if confirmed, may prove to be a valuable diagnostic aid in acute disseminated lupus erythematosus.

Dr. John F. Madden, St. Paul: I wish to thank everyone who discussed this paper. If it is possible to look into the future of work with acute disseminated lupus erythematosus and dermatomyositis, I think that in all probability muscle biopsies will not be used in differential diagnosis. The removal of muscle tissue for biopsy is a major surgical operation and should be avoided when possible, especially in a patient who is very ill. The Haserick phenomenon probably will be the only differential diagnostic aid needed in the future. The performance of this test does not disturb the patient. The L. E. cell seems to be purely incidental. The L. E. cells may be a few of the stronger remaining polymorphonuclear leukocytes which have resisted the toxin or whatever it may be that destroys the others and causes leukopenia and anemia in acute disseminated lupus erythematosus.

POIKILODERMA VASCULARE ATROPHICANS

Report of a Case Due to Exposure to Cold

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IN 1906 Jacobi [1] described a complex dermatologic disease characterized by telangiectasia, pigmentation and, later, capillary hemorrhages and atrophy, which he subsequently termed poikiloderma vasculare atrophicans.[2]

In a previous report [3] of a fatal case in which the lesions of poikiloderma vasculare atrophicans started after exposure to sunlight, we suggested the possibility that physical factors might be precipitating causes of this disease. Other authors published reports of cases in which there was a history of exposure to cold.[4] In the cases of Montgomery and O'Leary [5] and of Ingram [6] cold intensified the erythema. Zinsser [7] attributed the disease in his patients to injury in early life of the small blood vessels on the exposed parts of the body.

From the Boston City Hospital, Department of Dermatology and Syphilology, and the Mallory Institute of Pathology.

1. Jacobi, E.: Fall zur Diagnose (Poikilodermia vascularis atrophicans), Verhandl. d. deutsch. dermat. Gesellsch. **9**:321, 1907.

2. Jacobi, E.: Poikilodermia Atrophicans Vascularis, in Neisser, A., and Jacobi, E.: Ikonographia dermatologica, Berlin, Urban & Schwarzenberg, 1908, pt. 3, p. 95.

3. Downing, J. G.; Edelstein, J. M., and Fitzpatrick, T. B.: Poikiloderma Vasculare Atrophicans: Report of a Case with Observations at Autopsy, Arch. Dermat. & Syph. **56**:740 (Dec.) 1947.

4. (*a*) Taussig, L.: Poikiloderma Atrophicans Vasculare, Jacobi: Report of a Case with a Review of Recent Literature, Arch. Dermat. & Syph. **25**:882 (May) 1932. (*b*) Oulmann, L., in discussion on Taussig.[4a] (*c*) Bettmann: Ueber die Poikilodermia atrophicans vascularis, Arch. f. Dermat. u. Syph. **129**:101, 1921. (*d*) Bowman, K. M., and Clark, E. C.: A Case of Poikiloderma Atrophicans Vasculare, Arch. Dermat. & Syph. **15**:583 (May) 1927.

5. Montgomery, H., and O'Leary, P. A.: Poikiloderma Atrophicans Vasculare (Jacobi)? Arch. Dermat. & Syph. **25**:942 (May) 1932.

6. Ingram, J. T., and Stewart, M. J.: Dermato-Myositis and Poikilodermia, Brit. J. Dermat. **46**:53 (Feb.) 1934.

7. Zinsser, in Neisser, A., and Jacobi, E.: Ikonographica dermatologica, Berlin, Urban & Schwarzenberg, 1910, pt. 5, p. 219.

Kindler[8] reported a case following severe injuries from a motor accident. Many dermatologists expressed the view that the cutaneous picture of poikiloderma vasculare atrophicans might be the result of repeated insults to the skin from various factors.[9]

As a further proof of the effect of physical agents, the following case, in which repeated exposure to cold was definitely a factor, is reported.

REPORT OF A CASE

J. P., a 48 year old single, Greek-born iceman, first reported to the skin outpatient department of the Boston City Hospital on June 19, 1945, and was immediately admitted for study. He was very uncooperative but gave the following history. Approximately twenty-eight years before, he had first noted generalized dryness of the skin with "red spots" starting on the anterior upper left portion of the chest and progressing gradually over the years to involve the anterior aspect of the upper third of both thighs and the area over both anterior superior iliac crests. The condition progressed without remission and was associated with mild pruritus, particularly during the winter months. The patient had delivered ice for the past twenty-eight years and usually carried the load on his left shoulder (fig. 1). In the process of loading the ice onto his shoulder, he placed the cake of ice first on the anterior aspect of the upper third of either thigh or on the iliac crests and then hoisted it to the shoulder, usually the left one. He had never consulted a dermatologist prior to the present admission and did not bother to see a physician about his skin trouble because it was asymptomatic, except for mild pruritus. He denied roentgen, ultraviolet, local or internal therapy for the skin condition. He had consulted his local physician recently because of the development of an ulceration in the area involved over the left anterior shoulder.

Family History.—There was no family history of skin disease.

Social History.—The patient had always had the same job and according to his employers was reliable. He denied exposure to the sun and even in midsummer wore a coarse cotton shirt. For the past thirty years he had consumed over 2 pints (946 ml.) of whisky per day, plus a heavy intake of beer. His diet was inadequate in animal protein; milk, butter and green vegetables were never eaten; he lived mostly on alcoholic beverages and potatoes, occasionally meat. He ate nothing in the morning and had an occasional sandwich or meat and potatoes at various restaurants at night.

Past History.—He denied all previous medication except 17 "shots" of an unspecified type for syphilis in 1920. His weight had been constant for the past fifteen years. In 1922 he had pneumonia.

Review of Systems.—No joint or muscle pains were present; there were no tender or suppurating lymph nodes. There were no visual symptoms or tinnitus and no dyspnea, orthopnea or ankle edema.

Gastrointestinal Observations.—The patient was seen by his local physician in 1944 for a complaint of pain in the upper part of the abdomen (not described), and a roentgenographic series of the gastrointestinal tract revealed a duodenal ulcer and hypertrophic gastritis.

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8. Kindler, T.: Poikiloderma Atrophicans Vasculare, Jacobi, Proc. Roy. Soc. Med. **36**:619 (Sept.) 1943.

9. Oliver, E. A.: Mycosis Fungoides with Poikiloderma-like Symptoms, Arch. Dermat. & Syph. **33**:267 (Feb.) 1936.

Genitourinary Examination.—There was no dysuria or hematuria. The patient had had gonorrhea at least five times, the last attack having occurred in 1930.

Nervous System.—He denied any nervous breakdown, loss of memory or change in personality.

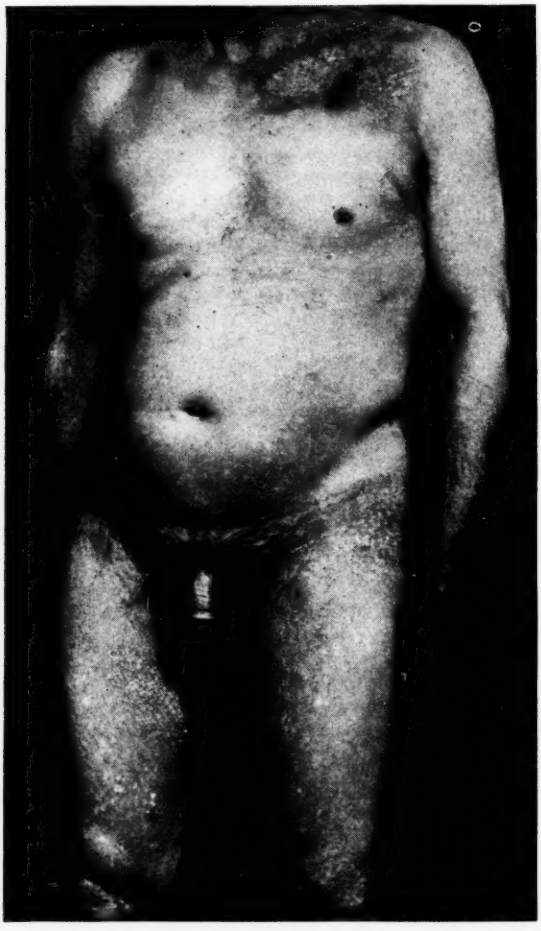

Fig. 1.—Note that the involved areas are the sites of maximum contact with ice.

Extremities.—He denied "shooting" pains down the legs, numbness or tingling of his legs.

Physical Examination.—Physical examination revealed a well developed, fairly well nourished man resting comfortably in bed. His temperature was 98.6 F.; his pulse rate, 80; respiration, 20 and blood pressure, 142 systolic and 80 diastolic.

Skin Distribution: There were no lesions on the scalp or face. On the anterior aspect of the left upper part of the chest there was an oval area of eruption, 10 cm. by 12 cm., which extended into the anterior axillary fold. Over each iliac crest, there was a 4 by 5 cm. area. The upper extremities were not involved. On the upper one third of the anterior aspect of the thighs there were symmetrically placed areas of involvement.

Description: The eruption consisted of an admixture of pigmentation, depigmentation, atrophy and a multitude of telangiectasias. The color varied from a deep red to a dark brown. Over the areas involved were fine, furfuraceous scales.

Fig. 2.—Pigmentation, depigmentation, atrophy, telangiectasia and furfuraceous scaling over the left upper portion of the chest.

In the shoulder lesion (fig. 2) there was a centrally placed 2 cm. area consisting of crusts and dried blood. There was also generalized dryness of the skin with no follicular hyperkeratosis.

The general physical examination otherwise was not remarkable.

Laboratory Observations.—Laboratory examination was limited because of the patient's failure to cooperate. The urine was acid, with no albumin or cells, and a specific gravity of 1.024. The white cell count was 9,000, with 64 per cent polymorphonuclear leukocytes, 32 per cent lymphocytes and 4 per cent monocytes. The nonprotein nitrogen in the plasma was 42 mg. per hundred cubic centimeters.

The sedimentation rate (Westergren) was 16 mm. The hematocrit reading was 49 per cent, and the icteric index, 8 units. Repeated serologic examination of the blood gave negative results.

Roentgenologic Examination.—The condition of the chest appeared normal on roentgenologic examination.

The patient refused to have lumbar puncture and special examinations.

Histopathologic Observations.—The biopsy specimen of skin from the left upper portion of the chest was fixed in Zenker's fluid, and serial sections were cut of the

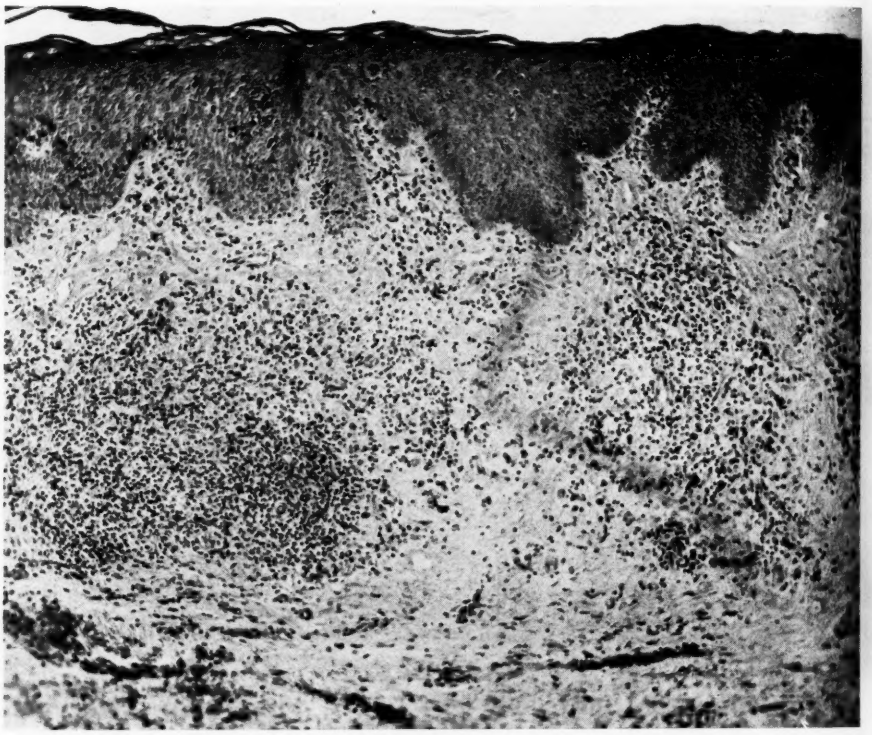

Fig. 3.—Note acanthosis and dense inflammatory infiltrate; eosin–methylene blue stain, × 104.

paraffin block. Sections were stained with eosin and methylene blue, by the Verhoeff technic for elastic tissue and by the Berlin blue method for demonstration of iron pigment.

In certain sections there was a surface layer of serum, fibrin and red blood corpuscles, infiltrated with leukocytes. Other sections showed a minimal to moderate degree of hyperkeratosis. The stratified squamous layer of epithelium showed acanthosis (fig. 3), with tonguelike projections into the underlying corium. In a rare section the epidermis was atrophied and the rete pegs considerably dimin-

ished in prominence. Those sections which revealed acanthosis and projections of the epithelium into the corium presented, occasionally, a thinned-out plate of squamous cells between the projections. The surface epithelium was flattened and its nuclei pyknotic. The major portion of the epidermis contained cells which had a pale, homogenous cytoplasm, a very distinct nucleus and usually two nucleoli. An occasional mitotic figure was seen. The chromatin of most nuclei was very finely dispersed and barely visible; however, in some basal cells the chromatin was present in large, coarse, easily visible clumps.

In places, the basal layer of the epidermis was invaded by lymphocytes and mononuclear cells which occupied the upper portion of the corium. The basement

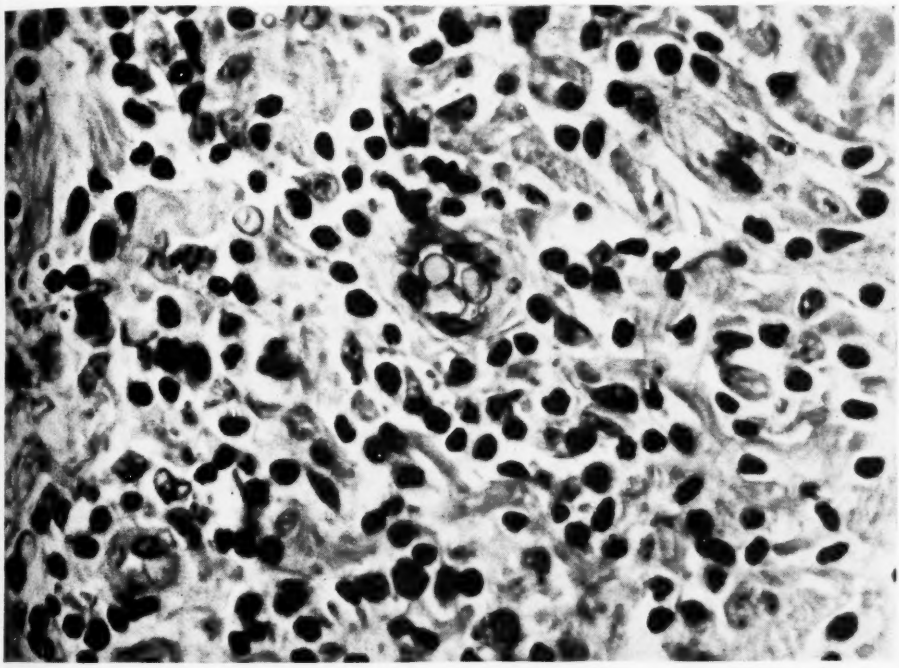

Fig. 4.—Note prominent capillaries and cellular infiltrate, composed of lymphocytes and rare plasma cell; eosin–methylene blue stain, × 772.

membrane of the basal layer was distinct and possibly somewhat accentuated in clarity. In certain sections the basement was frayed and split.

The upper part of the corium was the site of the following changes. There was a moderate degree of edema; there was dilatation and increased prominence of small vessels, with swelling of endothelium. There was a pronounced and somewhat diffuse infiltrate confined to the corium and separated from the under zone of the epidermis, comprised of lymphocytes, plasma cells, numerous histiocytes and mononuclear cells. An occasional multinucleated plasma cell was noted.

There was a field in the corium, in certain sections (fig. 4), which showed more clearly dilated, congested and prominent capillaries. In the very upper portion of

the corium there were scattered large chromatophores containing coarse, round, yellow-brown pigment globules; these cells, stained for iron, revealed no iron pigment. There was no iron pigment elsewhere in the section.

A very rare eosinophilic leukocyte was noted in the cellular infiltrate. There were no Reed-Sternberg cells seen. The hair follicles showed no evidence of disease. The collagen was fragmented and spread apart by edema. The ducts of sweat glands showed a swelling of the basement membrane and periductular edema which produced a fragmentation of muscle fibers.

Sections were stained by the Verhoeff method to demonstrate elastic tissue; the elastica showed a normal distribution and appearance, with no evidence of elastic tissue destruction.

There was no evidence of nerve involvement by the process.

COMMENTS

Sections from this case were submitted to F. Parker Jr., pathologist in chief, Mallory Institute of Pathology, who stated that the tissues showed a nonspecific inflammatory lesion of the skin and underlying corium.[10]

Fred D. Weidman, M.D., of the Department of Cutaneous Medicine, University of Pennsylvania, stated that the inflammatory infiltrate rather than the vascular and pigmentary changes, dominated the picture. Dr. Weidman further commented that certain features of the cellular infiltrate suggested mycosis fungoides but that there was insufficient evidence for such a diagnosis, especially in the absence of Reed-Sternberg cells. He concluded his comments with the statement that mycosis (or granuloma) fungoides might develop.[10]

Further opinions were sought from Hamilton Montgomery, M.D., of the Section on Dermatology, Mayo Clinic, who stated that the histopathologic changes were those of lymphoblastoma. Dr. Montgomery favored a diagnosis of mycosis fungoides.[10]

It was our impression that the histopathologic picture was most consistent with an inflammatory disease of the skin, as was evidenced by the findings of acanthosis, edema, congestion, endothelial swelling and the lymphocytic, plasma cell and histiocytic infiltrate. We further believed that there was no evidence of neoplasm, granuloma or lymphoblastoma.

Time alone, however, will tell whether this case will develop into a definite mycosis fungoides or one of the lymphoblastomas. Against these diagnoses is the fact that this patient was still alive and active at the time of writing. He was continuing his work as an iceman and apparently was not suffering any extreme discomfort, for he declined any further examination or treatment, despite repeated visits to his home.

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10. Personal communication to the authors, 1947.

CONCLUSION

A case of poikiloderma vasculare atrophicans is reported in which excessive contact with ice determined the site of the initial lesion. The case would make an interesting subject for discussion for a claim for compensation under the Workmen's Compensation Act. The histopathologic features are reviewed and considered to be consistent with an inflammatory disease of the skin.

520 Commonwealth Avenue, Boston (Dr. Downing).

Navajo Medical Center, Fort Defiance, Ariz. (Dr. Edelstein).

BERYLLIUM WINDOW RADIATIONS FOR SUPERFICIAL THERAPY

ANTHONY C. CIPOLLARO, M.D.
NEW YORK

DURING the past year there has been available to dermatologists a new type of x-ray machine which should be more flexible and more widely applicable than any single piece of x-ray apparatus thus far used in dermatology. The machine is shock proof and self rectified and emits in great intensities extremely soft radiations, even softer than grenz rays. The emission of great intensities of soft radiation is due to a special x-ray tube with a beryllium window.

Beryllium is a light metal with an atomic number of 4, a high melting point, of 1,285 C., and a specific gravity of 1.85. It has the appearance and hardness of steel even though it is slightly heavier than magnesium and lighter than aluminum. Beryllium is obtained from beryl ore, and there are only limited quantities of it. At present the metal is used in cast form. The beryllium window can be fused to glass or metal envelopes of x-ray tubes, and for this purpose the soldering method used is brazing with silver solder in a hydrogen atmosphere.[1]

Beryllium is pervious to roentgen rays, and at the same time it is sufficiently rigid and stable to withstand the ordinary uses to which an x-ray tube is subjected. Other light materials which are roentgen ray pervious, such as Lindemann glass, cellophane,® magnesium and aluminum, are too fragile for practical use.

The low linear absorption of beryllium makes it an ideal material for an x-ray tube window where high intensity and low penetrating radiations are desired.[2] Cellophane® or aluminum window tubes are rather transparent to roentgen rays and are used only in experimental laboratories because they are too fragile for ordinary uses. The

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From the New York Polyclinic Medical School and Hospital.

Read at the Sixty-Ninth Annual Meeting of the American Dermatological Association, Inc., Hot Springs, Va., May 28, 1949.

Much of the physical data were compiled by Mr. E. Dale Trout of the General Electric Corporation and have been checked by me with the use of a personally owned Victoreen r meter with a special nylon ionization chamber.

1. Brackney, H., and Atlee, Z. J.: Beryllium Windows for Evacuated X-ray Tubes, Rev. Scient. Instruments **14**:59, 1943.

2. Trout, E. D., and Atlee, Z. J.: Low Absorption Roentgen Ray Measurements from 10 to 250 Kilovolts, Am. J. Roentgenol. **47**:785, 1942.

permanent types of tubes having high roentgen ray transmission are made with windows of beryllium or Lindemann glass. The latter is also fragile, is subject to many changes and therefore is impractical. Cellophane® transmits the greatest amount of roentgen rays generated in a tube, and next in order are beryllium, aluminum, Lindemann glass and pyrex,® with beryllium having the greatest advantages. The problems of supply of the ore and of fusing the pure metal with glass or other metals have been overcome, and more tubes in the future will be made with this metal.

X-ray equipment with beryllium window tubes will not revolutionize superficial radiotherapy but will give to dermatologists an apparatus of great versatility and a type of radiation which is more suitable for everyday roentgen therapy of cutaneous lesions than that previously available. By the making of slight changes in voltage, current and filter in a matter of seconds, the optimum quality of the roentgen ray beam can be selected for lesions of various depths.

ADAPTABILITY

The low absorption characteristics of beryllium make it possible for one to use low voltage, long wavelength radiations simulating grenz rays. Such tubes can be energized with voltages as low as 5 kilovolts, and thus we have at our disposal a type of radiation similar to grenz rays. The half-value layer of grenz rays (8 kilovolts and 8 milliamperes) without filtration is 0.036 mm. of aluminum, while that of beryllium window radiations at 30 kilovolts and 1 milliampere without filtration is 0.06 mm. of aluminum. Thus, radiations produced with 30 kilovolts and a beryllium window are almost as soft as radiations produced with 8 kilovolts with the use of either Lindemann glass tubes or inverted extremely thin glass tubes. If it is desired to treat lesions which have a depth of 1 or 2 mm., radiations through a beryllium window tube are just as suitable as radiations from a grenz ray machine. If it is desired to utilize radiations which are a bit more penetrating, a filter of 0.25 mm. of aluminum may be employed.

Contact therapy is used to a limited degree by dermatologists. Radiations from beryllium window tubes can be utilized, and thus one can obtain the advantages ascribed to special equipment employed for close distance irradiation. The working distance with beryllium tubes may be a little greater than that with contact therapy machines, but this fact does not increase the depth dose to any appreciable degree because beryllium window radiations are so soft that increasing the skin-target distance by a few centimeters does not appreciably increase the depth dose. The radiations from contact therapy apparatus are relatively hard, and their half-value layer with the Chaoul tube at 50 kilovolts without additional filtration is approximately 2.4 mm. of

aluminum, and with the Philips tube, 0.3 mm. of aluminum; whereas with beryllium window radiations with the use of 50 kilovolts, 1 milliampere and no additional filter the half-value layer is 0.07 mm. of aluminum.

Conventional superficial therapy can be carried out with this new type of apparatus as efficiently and as effectively as with other types of standard x-ray apparatus, with one distinct advantage, and this is versatility. What I mean by versatility is that the apparatus delivers extremely soft radiations which affect mostly pathologic processes in the first few millimeters of tissue. All that needs to be done to increase the penetrability of the radiations is to interpose a filter of 0.25 to 3.0 mm. of aluminum between the tube and the skin. The half-value layer with 100 kilovolts and without filtration is 0.08 mm. of aluminum, and with a filter of 0.5 mm. of aluminum the half-value layer is 0.78 mm. of aluminum, which is comparable to that obtained with conventional roentgen ray apparatus. The soft radiations are there if one wishes to utilize them, and when a filter is interposed there is no sacrifice of time because the output with filters is comparable to that with the old type x-ray equipment heretofore used by dermatologists.

Thus it is seen that an apparatus having a beryllium window tube is an extremely flexible tool for dermatologic roentgen therapy and can be used for treating all the dermatoses that are ordinarily treated with roentgen rays, including the cutaneous neoplasms and scalp disorders requiring epilation. It has the essential mechanical and physical properties of grenz ray, contact and conventional superficial therapy apparatus. The penetration of the radiating beam is governed by the use of filters and by voltage. It has been pointed out that the half-value layer is 0.06 mm. of aluminum when one is using 30 kilovolts and no filter. By interposing a filter of 3.0 mm. of aluminum and using 100 kilovolts, one increases the half-value layer to 3.1 mm. of aluminum. Thus, the adaptability of an apparatus having an x-ray tube with a beryllium window makes it a most desirable unit for routine superficial therapy.

SELF RECTIFICATION

X-ray machines which are self rectified are ordinarily unsuitable for therapy. This situation is due to the fact that the anode becomes so hot after continuous use that the apparatus stops functioning and has to be cooled off before one continues. However, this statement does not hold true for the apparatus which I have been using during the past year and a half. I have given it rough usage both in treating patients in a busy office and in performing experimental work. The tube head is large, and it is cooled by a fan. The head contains the tube, the transformers and oil for cooling and insulation. There are no shockproof cables because the high tension circuit is enclosed and thoroughly insulated within the head.

The output of a beryllium window x-ray apparatus is much higher than is that of equipment used by dermatologists heretofore. At 30 kilovolts and 1 milliampere at a skin-focus distance of 15 cm. the output is 268 r per minute. At 100 kilovolts the output is 1,360 r per minute. With 100 kilovolts and 5 milliamperes and a distance of 7.5 cm. the output becomes approximately 25,000 r per minute. Such tremendous output is frightening. So far as we know now, there are no practical applications in dermatology for such tremendous doses. However, already there have been found uses for high intensity radiations in the fields of immunology, bacteriology and genetics. There are also numerous roentgenographic and industrial uses. The same precautions must be used with roentgen rays regardless of whether the intensity is high or low. The operator must be alert constantly. When short distances and high voltage and current are employed, filters should always be used.

A thin filter cuts down the output an amazing amount. At 100 kilovolts and 1 milliampere at 15 cm. distance with filtration 0.5 mm. of aluminum, the output is 83 r per minute in contrast to 1,360 r per minute with omission of the filter. With 3 mm. of aluminum, it is 18 r per minute. Thus far, I have used these low-penetrating radiations for those dermatoses and cutaneous malignant growths for which roentgen rays are ordinarily used with satisfactory results. When unfiltered roentgen rays were used, the total number of treatments required was greater by about 25 per cent than when the conventional type of superficial therapy units was used. The same point was noted in the treatment of basal cell epitheliomas. The reaction with large doses was intense but very superficial. However, when a filter of 0.25 to 0.5 mm. of aluminum was used, the results with beryllium window radiations were about the same as those with ordinary superficial units. A great deal more clinical experience is necessary before we can fully evaluate the efficacy of these long wavelength roentgen rays. However, I have not as yet epilated the scalps of children afflicted with tinea capitis. I doubt that unfiltered roentgen rays from a beryllium tube can be used practically for epilation. Some dermatologists have already successfully used filtered radiations from a beryllium window tube for scalp epilation. The unfiltered radiations are too soft to reach hair follicles unless tremendous surface doses are used. Animal experiments are now going on to determine this factor.

ERYTHEMA AND EPILATING DOSES

Radiations from beryllium window tubes follow the same patterns as do other soft radiations, namely, that the less penetrating radiations produce erythema with a smaller number of roentgens as measured in

air with a Victoreen r meter and a nylon chamber. For unfiltered radiation the erythema dose is about 200 r regardless of whether 30 or 100 kilovolts are employed. With filtered radiation the erythema dose is between 350 and 500 r, the amount depending on the thickness of the aluminum filter. With soft, unfiltered radiations the erythema dose is not the same as the epilating dose. At least 300 r of radiations having a half-value layer of 0.5 mm. of aluminum is required to produce epilation of the scalps of children with use of the Kienboeck-Adamson technic.

CALIBRATIONS

There is still some difficulty in measuring accurately the output in air of extreme soft radiations. Different physicists with different types of iontoquantimeters obtained significantly different readings with the same electrical factors, distances, areas and intensities. Even with different nylon chambers which have been calibrated against an open standard chamber, the readings vary significantly. This difficulty, I am sure, will be ironed out soon, especially if beryllium ionization chambers become available. Perhaps two reasons for these variations are air absorption and absorption of radiations in the wall of the nylon chambers.

RADIATION INTENSITY FIELD DISTRIBUTION

There is wide variation in the field of distribution of radiation, especially with shock-proof units. Tubes made with beryllium windows show about the same variations as other tubes. In a circular field of radiation, there may be as great a difference in intensity at a distance of 20 cm. from the center in one quadrant to another as 63 to 80—in other words, a difference in intensity of about 25 per cent.

THE INFLUENCE OF FIELD SIZE ON BACK SCATTER

It is significant that there is no appreciable increase in the dose due to back scatter regardless of the size of the field exposed between 3 and 20 cm. in diameter with beryllium window radiations of 30 to 100 kilovolts without filtration. The explanation for this observation is that long wavelength roentgen rays are absorbed in the first few millimeters of tissue. However, with an added filter the back scatter is as significant as with other types of equipment. With 100 kilovolts and 3 mm. of aluminum, the back scatter with a 3 cm. diameter field is 15 per cent, and with a 20 cm. diameter field it is 36 per cent. Incidentally, the "exit dose" is similarly affected. There is no appreciable exit dose without filtration, and with a filter of 3 mm. of aluminum the exit dose is the same as it is with conventional superficial apparatus and a filter of equal thickness.

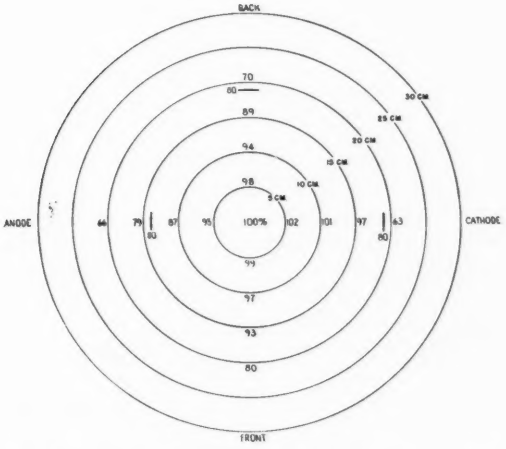

Fig. 1.—Radiation intensity distribution at a skin-focus distance of 30 cm. with the Maximar 100 at 100 kilovolts (peak) witihout filtration. The field of distribution is fairly uniform at a 20 cm. diameter except at the anode side of the tube.

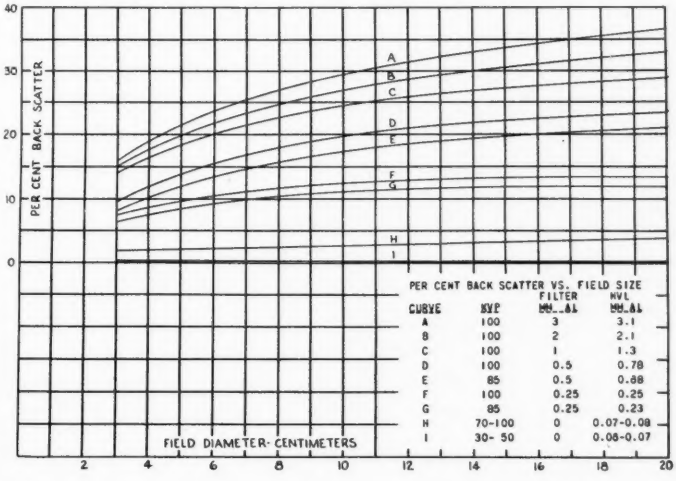

Fig. 2.—Data pertaining to back scatter. The larger the irradiated field and the harder the radiation, the greater the back scatter.

DEPTH DOSE

The tendency in dermatology during the past twenty years has been to utilize radiations of low penetrability. Unfiltered radiations from pyrex® tubes were of sufficient hardness to penetrate beyond the pathologic processes and even endanger underlying important structures or the skin on the opposite side of the treated area in cases of the face, hands and feet. On the other hand, radiations from grenz ray machines were so superficial in their effects that the entire pathologic process was not affected by the incident beam of radiation. The surface cells received an abundance of radiation sufficient to cause radiation sequelae, and the cells at a depth of 2 or 3 mm. were practically unaffected. Study

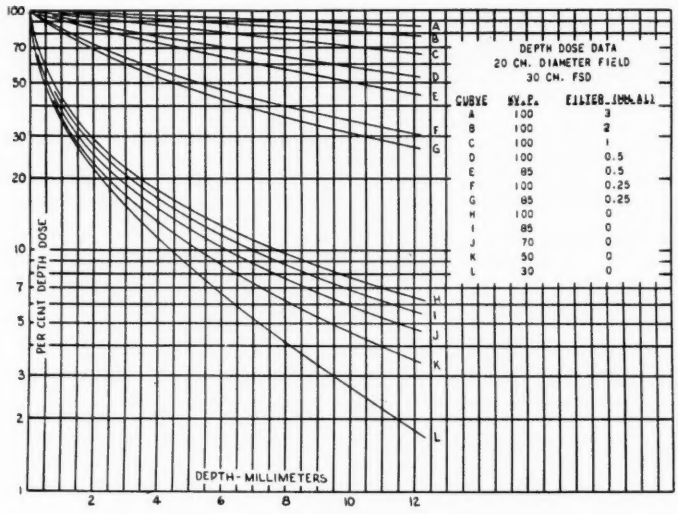

Fig. 3.—A graph which shows the depth dose of radiations from a beryllium window tube with kilovoltages varying from 30 to 100 kilovolts, with and without filtration. The half-value layer of each type of radiation is given.

of depth doses with radiations from beryllium window tubes with and without filters proved very interesting in this regard. On one extreme, let us consider for the moment the harder of the superficial radiations, those produced with a beryllium window tube using 100 kilovolts, 5 milliamperes and filtration of 3 mm. of aluminum, with a focus-skin distance of 30 cm. and a field diameter of 20 cm. If the incident beam at the surface of the skin is 100 r, at a depth of 12 mm. the depth dose is approximately 88 r. The depth dose becomes smaller as the field diameter narrows and as the focus-skin distance is decreased. Now let us consider for the moment a more superficial type of radiation, pro-

duced with a beryllium window tube using 30 kilovolts, 5 milliamperes and no filtration, with a focus-skin distance of 30 cm. and a field diameter of 20 cm. If the incident beam at the surface of the skin is 100 r, then at a depth of 12 mm. the depth dose is approximately 2 r and at 3 mm. depth the dose is 15 r. By varying the conditions of exposure, it is possible for one to obtain with one x-ray unit any desired depth dose, and these depth doses are the ones that meet all the exacting requirements of dermatologic roentgen therapy. Obviously, for lesions having a thickness of 3 mm. or more, one would not employ unfiltered roentgen rays from a beryllium window tube. Depth doses have been calculated for all voltages from 30 to 100 kilovolts, with and without filtration. It is not the object to record all these data in this paper.

It was my intention in this short presentation to record the high lights concerning beryllium window radiations. Pertinent data regarding the physics and the practical application of extremely long wavelength roentgen rays are presented. There is still much to be done. This presentation is just a starter. I can foresee fascinating possibilities in working with these soft radiations with a versatile apparatus, especially when the difficulties involved in obtaining accurate intensity measurements are overcome.

40 East Sixty-First Street.

Mr. E. Dale Trout and his associates of the General Electric Corporation cooperated in the presentation of these data.

ABSORPTION OF ROENTGEN RAYS WITH USE OF A BERYLLIUM WINDOW TUBE

M. F. ENGMAN Jr., M.D.
E. P. WEBER, M.D.
AND
W. G. ELLE
ST. LOUIS

ROENTGEN ray therapy of skin diseases, to the dermatologist, is like his right hand. M. F. Engman Sr. began using roentgen rays in 1904; Pusey, in 1902. A number of years ago, one of us (M. F. E. Jr.) was privileged to listen to a conversation between Engman and Pusey on the results obtained with roentgen rays in the years before the Coolidge tube was in use. Both agreed that the clinical results were better with the old equipment. They thought that probably the quality of roentgen rays was softer and that they were absorbed in the skin to a greater degree. Much attention was paid to roentgen ray quality at that time; quantity was largely a matter of shrewd guesswork. Since the early days, great advances have been made in study of the physics of roentgen irradiation, but we are still somewhat backward as regards actual knowledge of the biologic effects.

The dermatologist is mostly concerned with what happens in the outer 4 to 6 mm. of tissue exposed to therapeutic doses of roentgen rays. The type of x-ray machine most of us have been using produces radiation with a half-value layer of 1.0 to 1.5 mm. of aluminum. Softer radiation in the form of contact roentgen rays and grenz rays has been of limited use. Recently there has become available to dermatologists an x-ray tube with a beryllium window. The use of beryllium reduces the inherent filtration[1] to a minimum and therefore furnishes us with a quality of roentgen rays far different from that to which we have been accustomed. The biologic and clinical effects of this new type of x-ray apparatus are, to a great extent, unknown.

Read at the Sixty-Ninth Annual Meeting of the American Dermatological Association, Inc., at Hot Springs, Va., May 28, 1949.

1. Trout, E. D., and Atlee, Z. J.: Low Absorption Roentgen-Ray Measurements from 10 to 250 Kilovolts, Am. J. Roentgenol. **47**:785-790, 1942; Roentgen-Ray Measurements up to 400 Kilovolts Made with Beryllium Window Tubes, ibid. **50**:648-652, 1943.

In order to have some base line for further study of the clinical usefulness of this relatively unfiltered radiation, we have undertaken some preliminary studies of its absorption in the first 4 mm. of tissue, using polystyrene (density 1.05 to 1.08) as a phantom. The x-ray machine is the General Electric Maximar 100, incorporating a beryllium window.

IONIZATION CHAMBER

A black nylon thimble chamber was used with the Victoreen r meter. The walls of this chamber are the thinnest obtainable, so that absorption in the walls is reduced as much as is possible at this time. The correction factors for this source of error are not exactly known. For this reason, in our work we are using uncorrected measurements. Since our figures are all used for a comparative and relative purpose, this error need not be considered important. When even thin aluminum filters are introduced, the standard bakelite® chamber and the nylon chamber will agree within the limits of experimental error.

TABLE 1.—*Half-Value Layers at Various Peak Kilovoltages and Filtrations*

Peak Kilovoltage	Filter, Mm.	Half-Value Layer (Aluminum), Mm.
30	0	0.05
30	0.25	0.20
30	0.50	0.25
50	0	0.05
50	0.25	0.30
50	0.5	0.40
50	1.0	0.85
100	0	0.05
100	0.25	0.38
100	0.5	0.70
100	1.0	1.6

The nylon chamber was surrounded on three sides with polystyrene in order that back scatter would be included. Millimeter thick layers of polystyrene were placed in front of the chamber, thus acting as a filter. The thickness of the chamber remained an unavoidable source of possible error in the consideration of the depth dose.

RESULTS

Figure 1 represents a family of curves. The lower three are aluminum absorption curves. It is interesting to note (table 1) that the half-value layer at 30, 50 and 100 kilovolts (peak) is 0.05 mm. of aluminum with unfiltered roentgen rays. Figures for half-value layers with filtration of 0.25, 0.5 and 1.0 mm. of aluminum are given in table 1.

The upper five curves (fig. 1) represent the amount of roentgen rays absorbed in the first 4 mm. of tissue, polystyrene being used as a phantom. Even at 100 kilovolts (peak) without filtration, over half of the roentgen ray beam is absorbed. There is still greater absorption at peak kilovoltages of 50 and 30. The value of these curves as a guide

to probable biologic effect has been demonstrated at times. Quastler [2] used the rabbit ear in some biologic tests and found the "rabbit's ear curve" to be almost the same as the curve found by Quimby and Focht [3] on measurements with the extrapolation chamber. Both of the aforementioned reports were based on studies with contact x-ray apparatus.

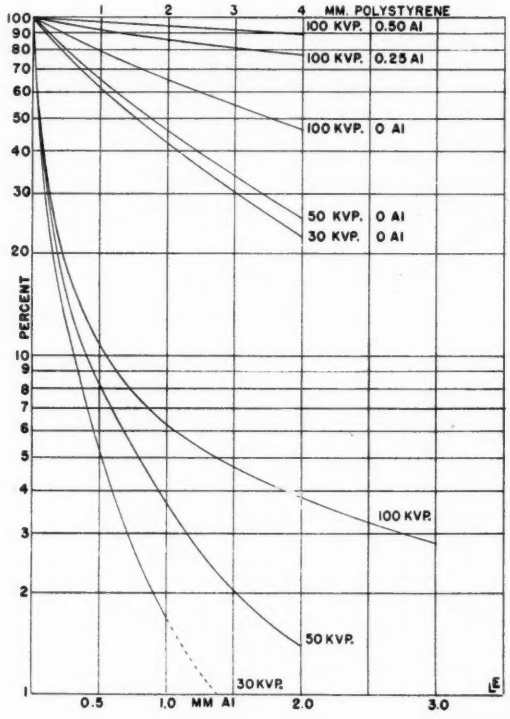

Fig. 1.—Lower curves, aluminum transmission. Upper curves, polystyrene (phantom) absorption.

In 1936 Andrews and Braestrup [4] published a study of measurements of depth doses, using water as a phantom and an inclined photographic

2. Quastler, H.: Depth Dose Measurements in Contact Roentgen Therapy on a Biological Test Object (Rabbit's Skin), Am. J. Roentgenol. **50**:669-676, 1943.

3. Quimby, E. H., and Focht, E. F.: Dosage Measurements in Contact Roentgen Therapy, Am. J. Roentgenol. **50**:653-668, 1943.

4. Andrews, G. C., and Braestrup, C. B.: Measurements of Depth Dose for Roentgen Therapy Used in Dermatologic Practice, Arch. Dermat. & Syph. **33**:446-456 (March) 1936.

film as a measuring device. Relative estimates were thus obtained of the amount of roentgen rays penetrating to various depths. The qualities of rays studied were those in common use at that time.

AIR ABSORPTION

Air absorption in glass-walled tubes having relatively high inherent filtration has generally been ignored. With these tubes the inverse

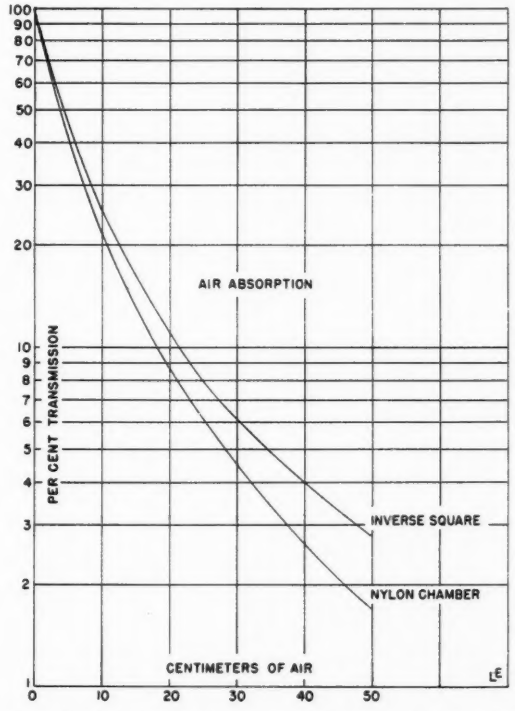

Fig. 2.—Actual nylon chamber measurement, compared with calculated inverse square curve.

square law can be used to determine the output at distances other than those measured with the ionization chamber.

Beryllium window tubes, with their high output of soft radiation, present a different problem of air absorption.[5]

Figure 2 represents air absorption with unfiltered roentgen rays. The curve for the nylon chamber is composed of measurements of actual

5. Day, F. H., and Taylor, L. S.: Absorption of X-Rays in Air, Radiology **52**:239-247, 1949.

percentages of transmission. The initial reading was 10 cm. from the target. The chamber was then advanced in 10 cm. steps to 50 cm. The inverse square curve was calculated from the initial point in 10 cm. steps.

BACK SCATTER

Ceresin wax (density 0.90 to 0.95) was used as a phantom to study back scatter (table 2) in gathering further data on the quality of radiation. At 50 and 100 kilovolts (peak) the back scatter was 2.4 per cent and 3.0 per cent. Even aluminum filters of 0.25 mm. thickness produced a rapid climb in the percentage of back scatter. Relatively soft roentgen rays give rise to secondary electrons having short range in tissues (Quimby [6]), which fact may, to some extent, account for the low back scatter figures for this type of radiation. Trout [7] stated that with unfiltered radiation back scatter is almost negligible at any voltage.

TABLE 2.—*Percentages of Back Scatter at Various Peak Kilovoltages and Filtrations*

Field Diameter, 10 Cm.		
Peak Kilovoltage	Filter, Mm.	Back Scatter, %
50	0	2.4
50	0.25	10.0
50	0.50	11.6
50	1.00	12.0
100	0	3.0
100	0.25	14.3
100	0.50	15.5
100	1.00	22.0

ERYTHEMA DOSE

We have not as yet collected sufficient data to determine what is the threshold erythema dose with unfiltered roentgen rays. The uncertainties of the erythema as a criterion for roentgen ray dosage are well known.[8] However, we are all familiar with the meaning of erythema dose as regards roentgen ray quality of half-value layers of 1.0 to 1.5 mm. of aluminum. The erythema dose of roentgen rays of a half-value layer of 0.05 mm. of aluminum has an entirely different meaning biologically, apart from its actual value in roentgens. This new biologic value we will have to learn by experience.

6. Quimby, E. H.: Dependence of the Biologic Reaction on Quality and Intensity of Radiation, in Glasser, O.; Quimby, E. H.; Taylor, L. S., and Weatherwax, J. L.: Physical Foundations of Radiology, New York, Paul B. Hoeber, Inc.. 1944, p. 318.

7. Trout, E. D.: Personal communication to the authors.

8. McKee, G. M., and Cipollaro, A. C.: X-Rays and Radium in the Treatment of Diseases of the Skin, ed. 4, Philadelphia, Lea & Febiger, 1946, p. 126.

COMMENTS

It is logical to assume [9] that the effects of roentgen rays depend largely on their absorption in the tissues one attempts to treat. Thus, the first 4 mm. of depth covers a large part of our interest in therapy of the skin, particularly as regards normal skin. Over five times as much of the unfiltered roentgen radiation as of the radiation filtered with 0.5 mm. of aluminum is absorbed in the first 4 mm. of skin. If quantitative absorption alone is a guide to therapeutic effectiveness, then the unfiltered rays should prove to be the radiation of choice. However, if back scatter can have some meaning with regard to an optimum therapeutic quality, perhaps entirely unfiltered radiation is not the best. It is possible that the unfiltered rays can be modified by being filtered through some material other than common metals and a better quality of roentgen radiation obtained for therapeutic purposes.

At a depth of from 4 to 6 mm. there lies a plexus of blood vessels which furnish circulation to the normal skin. Prolonged radiation of these vessels will result in chronic obliterative changes which are fundamental in the process of chronic, progressive roentgen atrophy. It seems probable that the less radiation these vessels receive in the course of roentgen therapy, the less danger there is of permanent damage to the skin. The epithelium and the upper and middle portions of the cutis absorb a relatively large part of the unfiltered roentgen ray beam. These tissues, especially the epithelium, have great powers of recuperation, and so it appears that there may be a greater margin of safety with relatively unfiltered roentgen rays.

ABSTRACT OF DISCUSSION OF PAPERS ON BERYLLIUM WINDOW RADIATIONS

DR. GEORGE C. ANDREWS, New York: The two papers just presented are commendable efforts to explain the advantages of the beryllium window tubes which permit the use of very soft radiation in addition to qualities ordinarily produced by conventional apparatus. The absorption of the beryllium window is about 0.1 mm. of aluminum. That of the old Coolidge tube before the era of shock-proof apparatus was about 0.2 mm. of aluminum.

One must not confuse the use of such soft radiation at anode-skin distances of several centimeters with contact therapy. The term contact therapy is now loosely applied in this country, but it was originally used for and should be restricted to irradiation by a tube with the anode in contact with, or at a few millimeters from, the skin, as with the Chaoul tube. The hard quality of radiation (half-value layer, 3.3 mm. of aluminum) produced by this tube has very little penetration because the target of the tube is directly on the skin, where it also acts as a filter. From the Philips tube the radiation is softer and the target-skin distance is 18 mm. Such short distances cannot be used with the beryllium window tubes. The inverse square law is the principle underlying

9. Bucky, G.: Grenz-Ray Therapy, in Glasser, O., and others: Medical Physics, Chicago, The Year Book Publishers, Inc., 1944, p. 512.

contact therapy. The short anode-skin distance means that hard radiation is absorbed almost completely in the upper 1 or 2 cm. of tissue. This action is similar to the absorption of the gamma rays from radium plaques and tubes applied a few millimeters from the skin.

As pointed out by Braestrup and me in 1936, measurements of depth dose in the upper 10 mm. of skin cannot be accurately made by even a nylon ionization chamber because the chamber itself has a finite diameter of at least 2 mm. To overcome this and other serious sources of error, we recommended photographic measurement with an inclined film apparatus. As a result of these studies, in 1936 we advised for dermatologic therapy homogeneous radiation of an effective wavelength of 0.9 angstrom units, produced at 50 kilovolts with proper filtration on ordinary superficial therapy machines. This gave 87 per cent absorption in the first centimeter of skin and 18 per cent in the first millimeter. You may remember that 90 per cent of Bucky's grenz rays are absorbed in the first millimeter, which means that they can exert little direct action on pathologic conditions deeper than 1 mm. A similar condition exists with the soft radiation from the beryllium window tubes. According to the tables of Drs. Cipollaro and Engman, about 70 per cent of the radiation produced at 100 kilovolts is absorbed in the upper 2 mm. of skin and 80 per cent in the upper 3 mm. of skin. At lower voltages the absorption in the upper 2 mm. is even greater. This means that such soft radiation can be used only for superficial dermatoses such as pruritus, eczema, neurodermatitis, warts and very superficial epitheliomas. For those diseases the technic and dosage are similar to those with grenz rays and Philips tube as a distance. Relatively large doses can be given with little danger of sequelae.

There are, to my knowledge, two types of beryllium window tubes on the market, namely, the Machlett and the General Electric. I have been using the Machlett tube for four years at voltages anywhere from 50 down to 5 kilovolts and for fifteen years used grenz rays (half-value layer, 0.36 mm. of aluminum) and have had two Philips contact machines for about five years. At 25 kilovolts with the Machlett beryllium window tube, the half-value layer is 0.05 mm. of aluminum, and at 50 kilovolts it is 0.16 mm. of aluminum, which figures compare with half-value layers of 0.06 mm. of aluminum for the General Electric beryllium window tube when run at 30 kilovolts and 0.07 mm. at 50 kilovolts. For the Philips tube, which has a thin glass window and plastic cap, the half-value layer at 45 kilovolts is 0.02 mm. of aluminum, which means that the radiation is softer than that from the General Electric beryllium window tube run at 30 kilovolts. If the Philips tube is used at 15 cm. distance the output and setup are similar to those for the Maximar. I was glad that Dr. Cipollaro said, "Obviously, for lesions having a thickness of 3 mm. or more, one would not employ unfiltered roentgen rays from a beryllium window tube." There is no advantage in having a beryllium window if you add a filter.

Before closing, I should like to say a few words about the erythema dose of soft radiation from beryllium window tubes. For the last four years my associates and I have been attempting to determine, with special timers measured in hundredths of a second, the erythema dose with this quality of radiation, and we have made some surprising discoveries. With this soft radiation, the erythema frequently appears within an hour and lasts for three to five days and then disappears, leaving pigmentation which persists for weeks. If one expects an erythema to appear a week or ten days after exposure, one may use sizable doses up to 1,000 r without producing any such erythema, and when one inspects the patient after a

week's interval one sees only hyperpigmentation. However, as little as 50 r will frequently produce within a day an erythema which will persist for four to five days and be followed by pigmentation. One explanation of these variations may be that the coefficient of absorption of keratin is greater than that of tissue in general.

DR. JOSEPH J. ELLER, New York: I used grenz rays for over fifteen years and should like to endorse the statements of the previous speakers. These rays should be used in only very superficial conditions of the skin. They are not usually effective in deeper conditions nor are they satisfactory in treatment of most epitheliomas of the skin. In a large series of skin cancers my associates and I had treated with these rays, most with large doses and some with enormous doses, our results proved to be most disappointing. A large majority did not retrogress completely, and, of some which did, most recurred. We could report a complete retrogression for only a few of the very superficial epitheliomas. I therefore have discontinued this therapy for cancerous lesions.

OUTCOME OF PREGNANCIES OF WOMEN TREATED WITH AQUEOUS PENICILLIN FOR EARLY INFECTIOUS SYPHILIS

Prevention of Prenatal Syphilis

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CHICAGO

THE ADMINISTRATION of penicillin to pregnant syphilitic women has made it possible to prevent prenatal syphilis in the great majority of infants.[1]

The next problem of practical interest concerning which we have now accumulated considerable experience is the question of the lasting effect of penicillin therapy for subsequent pregnancies. This problem may be formulated as follows: Does a woman who becomes pregnant after having had, by present day standards, adequate treatment with penicillin

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From the Chicago Intensive Treatment Center, Venereal Disease Control Program, Chicago Board of Health, in Cooperation with the United States Public Health Service.

1. Lentz, J. W.; Ingraham, N. R., Jr.; Beerman, H., and Stokes, J. H.: Penicillin in the Prevention and Treatment of Congenital Syphilis, J. A. M. A. **126**:408-413 (Oct. 14) 1944. Ingraham, N. R., Jr.; Stokes, J. H.; Beerman, H.; Lentz, J. W., and Wammock, V. S.: Penicillin Treatment of the Syphilitic Pregnant Woman, ibid. **130**:683-688 (March 16) 1946. Aron, H. C. S.; Barton, R. L., and Bauer, T. J.: Prenatal Syphilis: Its Prevention by Use of Penicillin in Treatment of Pregnant Women with Early Infectious Syphilis, Arch. Dermat. & Syph. **56**:349-356 (Sept.) 1947. Ingraham, N. R., Jr.: Prevention and Treatment of Prenatal Syphilis, Am. J. Med. **5**:693-701, 1948. Goodwin, M. S., and Moore, J. E.: Penicillin in Prevention of Prenatal Syphilis, J. A. M. A. **130**:688-694 (March 16) 1946.

for early infectious (dark field–positive) syphilis require re-treatment, or is it safe merely to observe the patient's clinical and serologic status during subsequent pregnancies? [2]

The present study reports the results of the outcome of all pregnancies in women treated for dark field–positive primary, secondary or relapsing syphilis with one of the following schedules:

1. Administration of 2,400,000 units of aqueous penicillin (amorphous) over a period of fifteen days: 120 intramuscular injections, 20,000 units each, every three hours
2. Administration of 4,800,000 units of aqueous penicillin G (crystalline) over a period of seven and one-half days: 60 intramuscular injections, 80,000 units each, every three hours
3. Administration of 4,800,000 units of aqueous penicillin G (crystalline) over a period of seven and one-half days: 90 intramuscular injections, 53,333 units each, every two hours

In schedules 2 and 3 the same type of penicillin G, in an identical total dose (4,800,000 units), was given over the same period (seven and one-half days) with minor variations in the number of doses, the individual dose and the time interval between injections. Therefore, the groups of women treated with schedules 2 and 3 have been combined. Thus, there are two groups for comparison in the present study:

A. Those patients given 2,400,000 units over fifteen days with a total of 160,000 units during twenty-four hours
B. Those given 4,800,000 units over seven and one-half days with a total of 640,000 units during twenty-four hours, i. e., four times as much per day as group A

All women in the study were pregnant at the time of treatment and/or became pregnant subsequent to treatment with one of the described schedules. This latter group of "subsequent pregnancies" includes patients who were treated during pregnancy and became pregnant again once or several times and women who were not pregnant at the time of treatment but thereafter became pregnant once or several times. No re-treatment was administered for these subsequent pregnancies.

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2. Ingraham, N. R., Jr.; Rose, E. K.; Stokes, J. H., and Beerman, H.: Retreatment of the Pregnant Woman for Syphilis Following Penicillin, Am. J. Obst. & Gynec. **56**:340-346, 1948. Goodwin, M. S., and Farber, M. S.: The Necessity for Treatment of Pregnant Syphilitic Women During Every Pregnancy, Am. J. Syph., Gonor. & Ven. Dis. **32**:409-417, 1948. Tucker, H. A.: Penicillin Syphilotherapy Administered Prior to Pregnancy: A Study of 111 Pregnancies During Which Additional Antisyphilitic Treatment Was Withheld, ibid. **33**:1-7, 1949. Bowen, J. H.; Cole, H. N.; Driver, J. R.; Light, R. C., and Rauschkolb, J. E.: Herxheimer Reactions in Penicillin Treatment of Syphilis in Pregnancy, Arch. Dermat. & Syph. **58**:735-739 (Dec.) 1948.

The study is concerned with a total of 206 pregnancies (in 149 women) which terminated before April 1, 1949. One hundred and thirty women were treated during pregnancy, 75 with schedule A and 55 with schedule B. Seventy-six pregnancies occurred subsequently, 39 after schedule A and 37 after schedule B. Schedule A was used from February 1945 to August 1946, for the treatment of 76 women; schedule B, from July 1946 to November 1947, for 73 women. Satisfactory information was obtained for the outcome of 203, or 98.5 per cent, of the total 206 pregnancies.

Of the 203 pregnancies of known outcome, 190 terminated in live births and 13 in fetal deaths (abortions, miscarriages or stillbirths). Two stillbirths were attributable to syphilis, as will be explained later in detail. According to the medical reports received, none of the remaining 11 fetal deaths were related to syphilis.

Three sets of twins are included in the 190 live births, there thus being a total of 193 live-born infants. Eight of these 193 infants died before the age of 90 days of causes not related to syphilis; 6 infants were observed for less than ninety days but were, clinically and serologically, free of syphilis during this period. Of the remaining 179 infants, 175 were observed for a minimum of sixteen weeks and a maximum of forty-six months and 4 infants were observed for less than sixteen weeks but more than ninety days (see tables 1 and 2).

The examination of the infants included repeated Kahn tests and complete physical examinations; roentgenograms of the long bones were taken when indicated (seventy-eight roentgenogram films of 60 infants).

Table 3 groups the data by the month of pregnancy during which treatment was started. Table 4 gives the data for pregnancies according to the number of months subsequent to treatment that delivery occurred.

Not 1 case of congenital syphilis was detected in the 78 living infants born of the women treated with 4,800,000 units of aqueous penicillin during seven and one-half days (group B). Seventy-seven infants were observed for more than sixteen weeks, and 1 infant for ninety-six days. One stillborn baby, delivered forty-seven days after therapy of the mother was concluded, was a male macerated fetus weighing 3¼ pounds (1,474 Gm.) and measuring 46 cm. There is a possibility that syphilis may have played some role in the unfavorable outcome of this pregnancy.

In the group of women treated with 2,400,000 units of aqueous penicillin over a period of fifteen days, there were 99 infants definitely free of syphilis, of whom 63 were delivered of mothers treated for dark field–positive syphilis during these pregnancies; 36 were the outcomes of subsequent pregnancies for which no re-treatment was given. With 3 exceptions, all infants were examined at 16 weeks of age or later.

Two infants were considered syphilitic:

The mother was a 20 year old Negro with the diagnosis of secondary relapsing syphilis, dark field–positive, with a Kahn titer of 80 units, who was treated from April 18 to May 3, 1945, while pregnant, with 2,400,000 units of aqueous penicillin (group A). In March 1949 this patient returned to Chicago with 2 children. Neither child exhibited any clinical signs of congenital or acquired syphilis. But the first child, a girl born Sept. 30, 1945, four months and twenty-seven days after the conclu-

TABLE 1.—*Outcome of Two Hundred and Six Pregnancies in 149 Syphilitic Women with Dark Field–Positive Lesions Treated with Aqueous Penicillin*

Outcome of Pregnancies	Grand Total			No. of Patients Pregnant at Time of Treatment			No. of Patients Pregnant Subsequent to Treatment		
	Total	A*	B†	Total	A	B	Total	A	B
No. of women treated	149	76	73	130	75	55	66	31	35
Total no. of pregnancies	206	114	92	130	75	55	76	39	37
Outcome unknown	3	2	1	1	1	..	2	1	1
Outcome known	203	112	91	129	74	55	74	38	36
Pregnancies terminated in fetal deaths‡	13	5	8	5	3	2	8	2	6
Pregnancies terminated in live births	190	107	83	124	71	53	66	36	30
Number of infants (3 sets of twins)	193	109	84	125	71	54	68	38	30

*Those in group A received 2,400,000 units of amorphous penicillin administered in one hundred and twenty doses of 20,000 units every three hours during fifteen days.
†Those in group B received 4,800,000 units of crystalline penicillin G administered during seven and one-half days in (*a*) sixty doses of 80,000 units every three hours and (*b*) ninety doses of 53,333 units every two hours.
‡Miscarriages, abortions and stillbirths.

TABLE 2.—*Status of 193 Infants Born of Syphilitic Women Treated with Aqueous Penicillin*

Status and Length of Time Observed	Grand Total			Mother Pregnant at Time of Treatment			Mother Pregnant Subsequent to Treatment		
	Total	A	B	Total	A	B	Total	A	B
Total no. of infants	193	109	84	125	71	54	68	38	30
Infants observed less than ninety days, no signs of syphilis	14	8	6	8	7	1	6	1	5
No. of deaths	8*	4	4	4	3*a	1*b	4	1*c	3*d
No. of living infants	6	4	2	4	4	..	2	..	2
Infants observed more than ninety days	179†	101	78	117	64	53	62	37	25
No. free of syphilis	177‡	99	78	116	63	53	61	36	25
No. with congenital syphilis	2	2	..	1	1	..	1	1	..

*(*a*) 1. Full term infant, breech presentation, prolapsed cord, asphyxia, died after one hour; autopsy—cerebral hemorrhage. 2. Eighth month premature baby, died third day; autopsy—meconium ileus. 3. Eighth month premature infant, died fifty-first day; autopsy—postaspiration pneumonitis, nonspecific enteritis. (*b*) Full term infant, second twin; age 35 days, operated on for pyloric stenosis; died thirty-seventh day. (*c*) Seventh month premature infant, died forty-seventh day; autopsy—endocarditis and pericarditis. (*d*) 1. Sixth month premature infant, died second day; autopsy—atelectasis neonatorum. 2. Full term infant, died second day; autopsy—congenital heart disease. 3. Eighth month premature hydrocephalus; craniotomy performed.
†175 observed more than 16 weeks.
‡Includes three deaths not related to syphilis: (1) full term infant, died aged 95 days; autopsy—nonepidemic encephalitis; (2) full term infant, died aged 5 months, 4 days; heat stroke, dehydration, acidosis (autopsy); (3) full term infant, died aged 14½ months, pulmonary tuberculosis.

sion of the mother's treatment, had a reaction to the Kahn test of 120 units on April 11, 1949, and of 160 units on April 21. The second child, a boy born March 17, 1947, or twenty-two and one-half months after the conclusion of treatment of his mother, had a Kahn titer of 40 units on April 11, 1949. After he had been treated with 3,500,000 units of penicillin injection in oil and wax, the Kahn titer on July 11,

TABLE 3.—*Outcome of Pregnancies in Women Pregnant at Time of Treatment, Grouped by Month of Gestation in Which Treatment Was Started*

Outcome of Pregnancy and Treatment Schedule	Total	Mo. of Gestation 1	2	3	4	5	6	7	8	9
Total no. of pregnancies (outcome known)	129	3	10	6	19	22	26	20	20	3
2,400,000 units of penicillin given in fifteen days	74	2	10	2	9	15	12	11	11	2
4,800,000 units of penicillin given in seven and one-half days	55	1	..	4	10	7	14	9	9	1
No. of pregnancies terminated in fetal deaths*	5	..	..	..	2	..	1	1	1	..
2,400,000 units of penicillin given in fifteen days	3	..	..	..	1	..	1	..	1	..
4,800,000 units of penicillin given in seven and one-half days	2	..	..	..	1	..	..	1	..	..
No. of pregnancies terminated in live births	124	3	10	6	17	22	25	19	19	3
No. of infants (1 set of twins)	125	3	10	6	17	23	25	19	19	3
2,400,000 units of penicillin given in fifteen days	71	2	10	2†	8‡	15§	11†	11	10†	2
4,800,000 units of penicillin given in seven and one-half days	54	1	..	4	9	8‖	14	8	9	1

		First Trimester	Second Trimester	Third Trimester
Total of pregnancies				
No.	129	19	67	43
Per cent	100.0	14.7	52.0	33.3
Pregnancies terminated in fetal deaths*				
No.	5	..	3	2
Per cent	100.0	..	60.0	40.0
Pregnancies terminated in live births				
No.	124	19	64	41
Per cent	100.0	15.3	51.6	33.1

* Miscarriages, abortions and stillbirths.
† Including 1 infant observed less than ninety days.
‡ Including 1 infant with congenital syphilis and 1 infant observed less than ninety days.
§ Including 3 infants who died within ninety days after birth.
‖ Including 1 infant who died within ninety days after birth.

TABLE 4.—*Outcome of Pregnancies in Women Pregnant Subsequent to Treatment, Grouped by Number of Months After Treatment Was Started That Delivery Occurred*

Outcome of Pregnancies	Grand Total			Number of Months 9-12			13-24			Over 24		
	Total	A	B	Total	A	B	Total	A	B	Total	A	B
Total of pregnancies (outcome known)												
Number	74	38	36	6	1	5	43	16	27	25	21	4
Per cent	100.0	100.0	100.0	8.1	2.6	13.9	58.1	42.1	75.0	33.8	55.3	11.1
No. of pregnancies terminated in fetal deaths*	8	2	6	1	..	1	6	1	5	1	1	..
Pregnancies terminated in live births	66	36	30	5	1	4	37	15	22	24	20	4
No. of infants (2 sets of twins)	68	38	30	5	1	4	37	15	22	26	22	4
Infants observed less than ninety days, no signs of syphilis	6	1	5	1	..	1	4	1	3	1	..	1
No. of deaths	4	1	3	..	..	..	3	1	2	1	..	1
No. of living infants	2	..	2	1	..	1	1	..	1	..	..	..
Infants observed more than ninety days	62	37	25	4	1	3	33	14	19	25	22	3
No. free of syphilis	61	36	25	4	1	3	32	13	19	25	22	3
No. with congenital syphilis	1	1	..	..	..	..	1	1	..	..	..	..

* Miscarriages, abortions and stillbirths.

1949, was still 40 units. The diagnosis of congenital syphilis is certainly justified for the older child; the possibility of acquired syphilis cannot be denied for the younger child, but the probability of congenital syphilis appears to be greater.

In addition to these cases of congenital syphilis in the group of patients treated with 2,400,000 units of penicillin over a period of fifteen days, there is recorded 1 case of stillbirth:

The mother was given a diagnosis of dark field–positive secondary syphilis, with a reaction to the Kahn test of 80 units; delivery was due in six to eight weeks. Thirty-five days after conclusion of therapy, she delivered a full term stillborn infant with the diagnosis of intrapartum death. The autopsy record revealed petechial hemorrhages in heart and lungs, atelectasis and splenomegaly. The mother had a positive reaction to the Kahn test of 40 units four weeks before and four weeks after delivery. Thirty-seven days after delivery of the stillborn infant, and ten weeks after termination of treatment, the mother was re-treated for relapsing secondary syphilis with eroded papules, with a Kahn titer of 80 units.

This case of a stillborn infant is regarded as probably related to syphilis.

It is assumed that the incidence of prenatal syphilis is the highest when treatment of the pregnant woman starts late in pregnancy.[3] Of the 130 women treated for dark field–positive lesions during pregnancy, 26 women started penicillin therapy as late in pregnancy as eleven to fifty-eight days before delivery. Four patients were delivered one to ten days after therapy was concluded; 9, eleven to thirty days afterward, and 13, thirty-one to fifty days afterward.

In this group there were no cases of congenital syphilis; there were 2 stillbirths (7.7 per cent) recorded as possibly related to syphilis, with the infants delivered forty-seven and thirty-five days after conclusion of therapy; the remaining 24 infants (92.3 per cent) were definitely free of syphilis. Twenty-one of these infants were observed for longer than one year (twelve to forty-four months), 1 infant for seven and one-half and 1 for four and one-half months. One infant who had been examined six times previously died of encephalitis at the age of ninety-five days; previous examinations and autopsy report revealed no indication of syphilis.

In contrast to the favorable outcome of the pregnancies after complete treatment with 4,800,000 units of penicillin (group B), it appears of interest to report the following observation on a woman who was started on the same schedule B in her ninth month of pregnancy but could not be given more than 2,000,000 units of penicillin before she delivered a female infant. The mother received the balance of 2,800,000 units of

3. Cross, J. B.; McCain, J. R., and Heyman, A.: The Use of Crystalline Penicillin G in the Treatment of Syphilis in Pregnancy, Am. J. Obst. & Gynec. **57**:461-465, 1949.

penicillin after delivery and remained cured of syphilis. The infant had congenital syphilis. Because of the incomplete treatment with penicillin during pregnancy, this case could not be included in the tabulated cases.

SUMMARY

The present study is based on the information obtained for the outcome of 203 pregnancies of 147 penicillin-treated syphilitic women in whom the presence of Treponema pallidum was demonstrated before treatment. One hundred and twenty-nine of these women were treated during pregnancy; 74 pregnancies started after conclusion of therapy; no treatment was given during the subsequent pregnancies.

There was not 1 case of congenital syphilis in the 78 living infants delivered of women who were treated with 4,800,000 units of aqueous crystalline penicillin G given during seven and one-half days. One stillbirth was possibly attributable to syphilis.

Not quite so favorable were the results in the group of women treated with 2,400,000 units of aqueous amorphous penicillin given over a period of fifteen days. Of the total of 99 living infants, 97 were definitely free of syphilis; 2 infants from the same mother were syphilitic. In addition, 1 stillborn infant in this group was probably syphilitic.

Twenty-six pregnant women with dark field–positive lesions completed treatment as late as one to fifty days before delivery. Twenty-four, or 92.3 per cent, of these pregnancies terminated in the birth of healthy infants definitely free of syphilis; no cases of congenital syphilis were found; two pregnancies, or 7.7 per cent, terminated in stillbirths, possibly related to syphilis.

In pregnant women with early infectious syphilis, the treatment schedule of 640,000 units of crystalline penicillin G every twenty-four hours over seven and one-half days appears to prevent congenital syphilis with somewhat greater certainty than the schedule of 160,000 units of amorphous penicillin in twenty-four hours over fifteen days.

SHIELDING OF SKIN AGAINST ROENTGEN RADIATION BY PLASTIC COMPOUNDS

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LOS ANGELES

DURING the treatment of a cutaneous lesion with roentgen rays it is customary to shield the surrounding normal tissues with a sheet of a heavy metal, such as lead or tin, or a sheet of rubber containing a high proportion of such a metal. By means of scissors, openings of appropriate shape are cut in this material to fit the irregularities in the contour of the lesion. It is sometimes necessary to apply the shield to the lesion many times during the cutting of the opening before an accurately fitting outline can be secured, and if too much is cut away in any spot a new beginning must be made. Dermatologists soon acquire a few hundred small lead sheets with irregular openings, among which a hopeful search is conducted for one suitable for any new lesion presented for treatment. It is surprising how rarely this goal is attained.

If it is to furnish adequate protection, sheet lead should be about 1 mm. in thickness. Such a sheet is somewhat difficult to adapt by bending to fit into many areas; for example, in the nasolabial fold it cannot easily assume the necessary conical shape. After it is adequately fitted it must be held in place by strips of adhesive plaster applied to its surface and extending beyond its periphery onto the skin. Such peripheral support alone is not ideal; even though the borders remain fixed a small motion of the patient's muscles, such as a facial grimace, may destroy the accurate relation of the lesion to the central opening. If the supporting tapes are adjusted more tightly the hard surfaces of the metal and the roughly cut edges of the opening may cause the patient discomfort.

It has undoubtedly occurred to a number of workers that if a plastic, moldable substance somewhat like putty or modeling clay could be prepared with a powdered heavy metal as the principal ingredient many of these difficulties could be obviated. Fuhs [1] in Vienna is said to have utilized plaster of lead oleate (diachylon plaster) for this purpose as early as 1929.

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1. Winer, L. H.: Personal communication to the author.

Kaldeck [2] recently described a "lead-containing clay" for shielding purposes which contained 77 per cent lead in the form of a "fine lead powder." The remainder was composed of petrolatum U. S. P., 9 per cent; plastic clay (as used in toy sets) 5 per cent, and talcum powder, 9 per cent. The resulting mass was said to be "lead gray, nonsticky, slightly harder than soft putty, easily molded at room temperature, nonelastic and nonresilient."

An attempt was made to duplicate Kaldeck's formula, but it was not possible for me to obtain through commercial channels the "fine lead powder" described by him. In reply to an inquiry he stated that "fine lead powder may be obtained by filing a bar or sheet of lead down to a powder." It is likely that but few practitioners will utilize a method which entails such a difficult task; lead is so soft that by clogging the teeth it renders a file useless after but a few strokes. It is unnecessary, moreover, that the lead be in the metallic state; any salt of any heavy metal will serve the same purpose. It is necessary, of course, to use a slightly thicker layer of such a compound to compensate for the elements of lower atomic weight which it contains.

I wish to present a method of shielding which has been found to be quicker, cleaner, more accurate, more comfortable and less expensive than the procedures in general use. A plastic clay containing a large proportion of heavy metal will be described, the formula having been selected to afford several noteworthy advantages. The manner of using this material will be discussed in detail.

PLASTIC HEAVY METAL CLAY

It was apparent that a putty-like mass, such as was desired, should result from mixing a powdered salt of a heavy metal intimately with an oily liquid or semisolid vehicle. While any salt of any element having a high atomic weight deserved theoretic consideration as well as the element itself, the ultimate selection of the most appropriate substance proved very easy. In the elemental state most metals of large atomic weight are gray and would yield a compound of "soiled" appearance. Any fragments of such a preparation adhering to the hands of the operator or the patient's skin would be more objectionable than those of a preparation in which a white salt was used. Of the chemical elements possessing an atomic weight greater than 150, all but four—mercury, tungsten, lead and bismuth—were immediately eliminated because they are rare and expensive. The danger to the operator of toxicity from salts of mercury or lead by absorption through the skin seemed great enough to exclude them if others less toxic could be made to serve.

2. Kaldeck, R.: Lead-Containing Clay for Shielding in Roentgen Ray Treatment of the Skin, Arch. Dermat. & Syph. **59**:665 (June) 1949.

Bismuth was chosen over tungsten because it is cheaper and several of its salts are commercially available in the form of a fine white powder. Its atomic weight (209) compared with that of tungsten (184) adds to its efficiency for the present purpose. In addition, bismuth has the advantage of having been used internally as well as topically for so many years that its low toxicity seems well established. Bismuth subnitrate was the final choice because of its high content of metallic bismuth (59 per cent), which is considerably higher than that of the other common commercially available bismuth salt, the subcarbonate (40 per cent).

The search for the ideal vehicle for admixture with the selected powder was facilitated somewhat by the knowledge that if it had any tendency to evaporate, the resulting plastic clay would gradually harden and become useless or need readjustment. Of several nonevaporating vehicles tested, glycerin, carbowax,® liquid petrolatum and petrolatum were found to yield a sort of ointment, that is, a substance with more tendency to adhere to the skin than to itself; any attempt to use such a mixture resulted in a residual coating on the skin which was difficult to remove. Several plastic rubber mixtures and rubber cements were tried without success because these substances soon hardened.

When anhydrous wool fat is used, however, the resulting putty has many desirable features; its only imperfection is a slightly higher degree of "stickiness" when it is unusually warm. It is doubtful that this feature can ever be entirely obviated since all semisolids have this characteristic to a greater or lesser extent. Further attempts will be made to improve the formula in this regard; at this time it seems best simply to recommend the incorporation of a slightly higher percentage of the powder in the formula in hot climates or during hot weather.

The formula for heavy metal plastic clay [3] is as follows:

Bismuth subnitrate powder.....84 per cent
Anhydrous wool fat.....16 per cent
(Note well: Hydrous wool fat is entirely unsatisfactory for this purpose, since evaporation of its water causes the clay to harden.)

Some variation is to be expected in the consistency of wool fat due to differences in the strains of animals from which the wool is obtained, the season of the year in which the wool is sheared and the various methods of manufacture. It is, therefore, not possible to state the exact percentage of wool fat which will yield a product of ideal consistency, but from 13 to 16 per cent by weight will be found to be adequate. It is best to weigh out wool fat to the extent of 16 per cent of the total

3. All materials were supplied and the formula was developed through the cooperation of Gavin Herbert & Company, Pharmacists, 3875 Wilshire Boulevard, Los Angeles 5.

weight of clay desired, heat it over a water bath and add the powdered ingredient in small portions while mixing thoroughly. The mass is allowed to cool to room temperature and taken into the hands of the operator. Additional small amounts of the powder are then kneaded in until the desired consistency is attained.

CALIBRATION

Figure 1 offers photographic proof of the efficiency of plastic heavy metal clay of the formula given in shielding against roentgen radiation. A photographic plate was arranged so that a portion was shielded by a tapered wedge of the clay varying from 0 to 3 mm. in thickness; an adjoining portion was shielded by a strip of sheet lead uniformly 1 mm. in thickness. The entire plate was exposed to 500 r at 85 kilovolts

Fig. 1.—Efficiency of heavy metal clay compared to lead in stopping roentgen radiation.

without filtration. It is apparent that approximately one and one-half times as thick a layer of clay is needed as of metallic lead. This observation compares favorably with the calculation of theoretic efficiency made from a comparison of the atomic weights of the ingredients of the clay with the atomic weight of lead (62.2 per cent as efficient).

It soon became apparent, moreover, that the plastic clay was much easier to handle in a layer at least 5 mm. in thickness; otherwise it was difficult to prevent the formation during handling of spots too thin for safety in shielding. A 5 mm. thickness is equivalent to 3.2 mm. of lead and affords an ample safety factor. It is necessary to recalculate by the method of inverse squares the output of the machine at the slightly greater distance needed when a 5 mm. thick clay shielding is used; for example, 6.3 per cent more radiation time must be allowed at 131 mm. than at 127 mm. (5 inches) if the lesion is to receive an equivalent dose.

DESCRIPTION OF THE MATERIAL

In physical properties the product is a white, plastic, putty-like mass which may be caused to assume any shape desired with but small pressure; this shape is then retained until further pressure is applied. The clay may be rolled between the hands into a ball (fig. 2) and kneaded

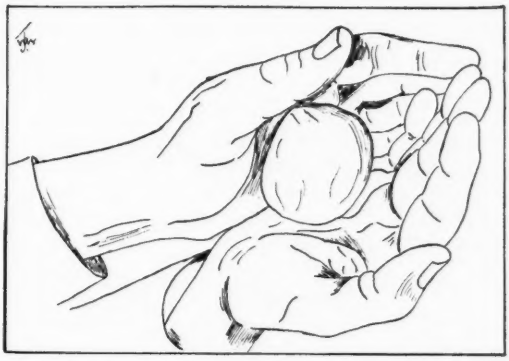

Fig. 2.—Plastic heavy metal clay may be rolled into a ball between the hands.

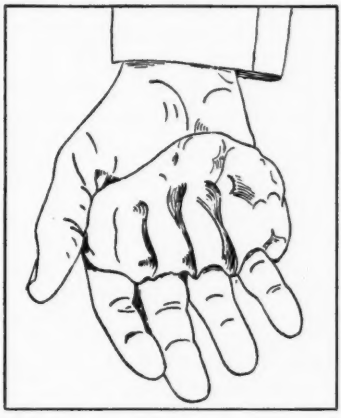

Fig. 3.—Plastic clay is of the same consistency as firm putty. In the test illustrated it should not adhere to the fingers.

in the fingers for several minutes before it begins to stick to them (fig. 3). If it is too warm the preparation will prove to be too sticky; it is advisable to keep some powdered bismuth subnitrate at hand in a shaker-top container to sprinkle on the hands, if necessary. It may be necessary also to powder the patient's skin lightly when the clay is warm to prevent

difficulty in removing all traces of it after its use. By each such operation a little more powder is added to the clay, and thus its consistency is slowly adjusted to the summer temperature.

It has also been observed that any particular portion of clay becomes more plastic and sticky with every few weeks of use even at the same temperature. This is due to the fact that every time it is handled by the operator or applied to a patient's skin it acquires a little sebaceous material which changes the percentage of "wool fat" present. The use of the powder is thus a necessary readjustment occasionally.

METHODS OF USE

The simplest method of using the material consists in rolling it into a rough cylinder between the palms, coiling this cylinder around the lesion and flattening it from within outward with the fingers to a thickness of about 5 mm. (fig. 4). A closer approximation to the borders of the lesion may be obtained if desired by rolling the mass inward with the fingers; the reverse is as easily accomplished.

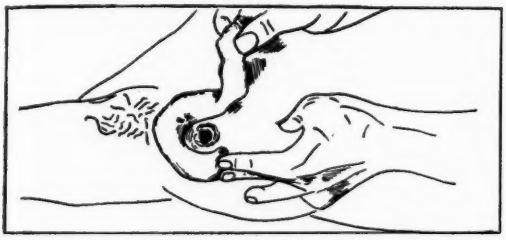

Fig. 4.—Illustrating the simplest method of shielding with plastic clay. A rough cylinder is formed by rolling the clay between the hands and is curled about the lesion, in this case a granuloma just below the axilla. The clay is then flattened by the hands to a thickness of about 5 mm.

Shaping the orifice is facilitated at times by using any dull instrument such as a knife handle or the wide tip of a pair of bandage scissors. A sufficient area around the lesion can usually be shielded in this manner to allow the exposure to be made safely through a properly selected cone. At times it may be necessary to add another ring of flattened clay circumferentially to increase the diameter of the shielded area.

A "compression paddle" similar to that in current use for flattening balls of ground meat intended for sandwiches (as illustrated in figure 5) has proved to afford a most convenient method of shaping plastic clay. A ball of clay is placed between two sheets of cellophane® or waxed paper (fig. 5 *B*) and compressed into a disk about 5 inches (12.7 cm.) in diameter (and 3/16 inch [5 mm.] in thickness). A plastic cloth such as koroseal® is somewhat preferable since it can be used many times before being discarded. The top cloth is removed easily without disturbing the disk if it is doubled sharply back on itself and pulled off in a direction parallel to the surface of the disk. The diagram (fig. 5 *D*) is misleading in this respect since it shows the force being exerted more nearly at right angles to the surface of the disk; this will distort the clay unduly.

A metal tube approximately the size of the lesion is now pressed firmly into the center of the disk and rotated until it is felt both to be free and to have come in

contact with the wood of the paddle beneath (fig. 5 *E*). The clay disk together with the central cut-out portion and the second cloth, is placed over the lesion in the approximate position and gently adapted to the skin, pressure being avoided at the center. When the second cloth is now removed it is easy to bring with it the

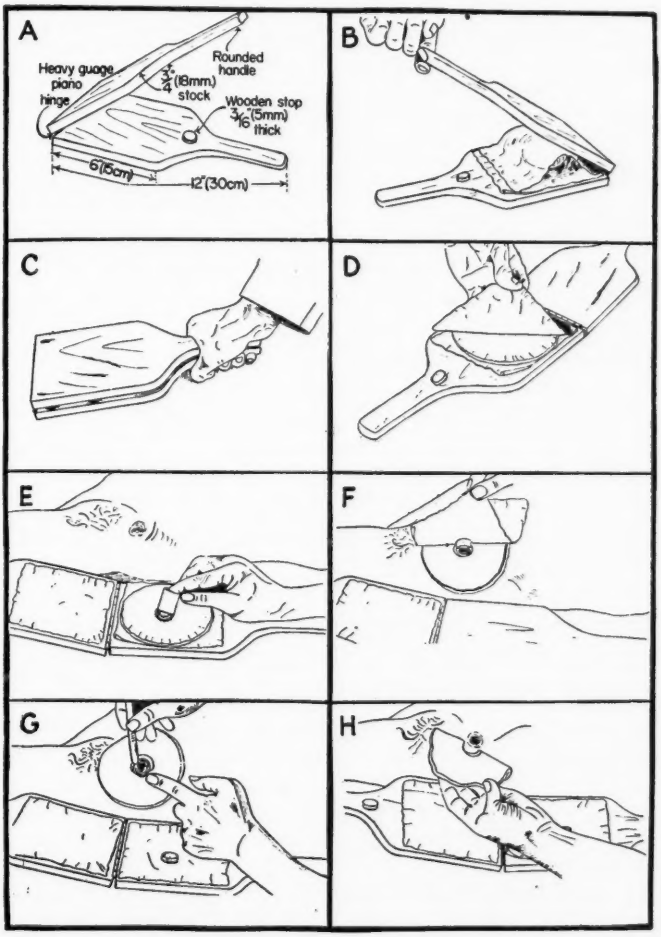

Fig. 5.—*A*, details of construction of a compression paddle for use with plastic clay. *B*, a ball of clay is placed in the paddle between two sheets of plastic cloth or cellophane.® *C*, the clay is compressed into a disk 5 mm. in thickness. *D*, the paddle is opened and the top cloth removed. *E*, a metal tube of appropriate size is pressed into the center of the clay disk. *F*, the clay disk is placed over the lesion in the approximate position. The remaining cloth is now removed, bringing with it the central cut-out portion. *G*, the borders of the opening are adjusted by simple pressure of the fingers or blunt instruments. *H*, after exposure to radiation, the clay is removed, rolled again into a ball and compressed in the paddle ready for use again.

central cut-out portion of clay (fig. 5 *F*). The borders of the opening are adjusted by simple pressure of the fingers or blunt instruments to the contours of the lesion (fig. 5 *G*). Bits of clay may be added or taken away as desired.

After the exposure to radiation has been completed the clay is removed (fig. 5 *H*), rolled again into a ball, placed between the cloths and compressed in the paddle ready for use again.

Intraoral Shielding.—When lesions on the cheek or lips are treated it is easy to shield the gums by interposing a layer of plastic bismuth clay. A ball of appropriate size is somewhat flattened and placed between the teeth and the cheek or lips. After the mouth is closed, pressure exerted externally causes the clay to adapt itself to the contours and spread adequately to the periphery of the cavity without the discomfort to the patient usually attendant when a sheet of lead is similarly used. The clay is almost tasteless, and after its removal it is necessary simply to rinse the mouth with water. The clay may also be washed with water before being put away for future use.

SUMMARY AND CONCLUSIONS

A plastic, putty-like clay containing 84 per cent bismuth subnitrate and 16 per cent anhydrous wool fat is recommended for shielding the surrounding normal skin while a lesion is treated by roentgen radiation.

This substance is 62 per cent as efficient in stopping radiation as is pure lead; hence a layer one and one-half times as thick is equivalent. For ease in handling, 5 mm. is the preferable thickness; this is equivalent in shielding efficiency to 3.2 mm. of lead.

A method of forming a disk of the clay in a compression paddle is described, with details of the manner of using it. Simple pressure of the fingers serves to increase or decrease the size of the opening in relation to the lesion, resulting in easy and accurate adaptation.

There is no waste in using this method since the original quantity of clay can be used indefinitely.

3875 Wilshire Boulevard (5).

DERMATOLOGIC ASPECTS OF INSECT REPELLENTS AND TOXICANTS

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CINCINNATI

PERHAPS it is not well known among physicians that insects were present and well established on this earth long before man came. Dermatologists have taken some minor roles in the long struggle between insects and man. However, in the modern phase of the investigative aspects,[1] dermatologists have an opportunity to play some major parts. Chemical control of insects is a definite part of the program of what I like to call modern preventive dermatology and certainly, of course, of global dermatology.

There is considerable interest in the amazing developments of new chemical agents for the control of insects. The general concepts have been summarized by Frear[2]: "Lyrical claims and hysterical warnings have largely given way to sensible recommendations for the safe use of new substances. It has been determined that none of them is a cure all but that each will find a useful place along with the older established materials."

Some recent interest in this field of the chemical control of insects has been shown already by dermatologists in the development of the technics of mass screening tests with regard to irritation of the skin,[3]

Read before the Section on Dermatology and Syphilology at the Ninety-Eighth Annual Session of the American Medical Association, Atlantic City, N. J., June 8, 1949.

From the Department of Dermatology and Syphilology and the Kettering Laboratory of Applied Physiology of the University of Cincinnati College of Medicine.

1. (*a*) Fourth International Congress on Tropical Medicine and Malaria, Section XII, Medical and Veterinary Entomology, Washington, D. C., May 1948. (*b*) King, W. V.: Some Recent Work on Newer Insecticides, Am. J. Trop. Med. **28**:487, 1948.

2. Frear, Donald E. H.: Chemistry of Insecticides, Fungicides and Herbicides, ed. 2, New York, D. Van Nostrand Company, Inc., 1948.

3. Sulzberger, M. B.; Baer, R.; Kanof, A., and Lowenberg, C.: Methods for Rapid Evaluation of the Beneficial and Harmful Effects of Agents Applied to Human Skin, J. Invest. Dermat. **7**:227, 1946.

the clinical applications of recently developed miticides,[4] the general clinical applications of repellents and insecticides,[5] clarification of the picture of reactions from flea bites,[6] and the study of the reaction of lichen urticatus[7] and the description of actual contact dermatitis from insects.

For the practical concern of dermatologists, the chemical control of insects may be divided into three essential phases: (1) repellent activity, (2) attractant activity and (3) toxicant activity. It would seem that such concepts should be obvious and simple, and yet indeed they appear to be very complex, and entomologists continue to work on each one of these in regard to the mechanisms of detailed approaches and reactions.

The general clinical aspects of the use of repellents in dermatology have been detailed before.[5a] It has been shown that topical application and impregnation of clothing have definite value in the prevention of the bites of those arthropods of dermatologic interest such as mosquitoes, flies, fleas and chiggers. Repellents are to be used with due regard to the period of protection and the area protected.

As regards the chemical repellents, the highly specialized sensory receptors of olfaction and gustation of the insect are concerned.[8] For the use of these substances on man, studies in physiology of the skin in regard to repellency are important. Briefly, some factors include sweating (dry skin may increase time of repellency), creep (movement of the repellent along sulci of the surface), absorption of substances by the skin, evaporation of them from the skin, oxidation or change in their chemical composition by the skin, the degree of mechanical application required for the repellent and the natural attraction presented by the host in the form of the skin soil or products of sweat or sebaceous gland

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4. (*a*) Wooldridge, W. E.: The Gammaisomer of Hexachlorocyclohexane in the Treatment of Scabies, J. Invest. Dermat. **10**:363, 1948. (*b*) Cannon, A. B., and McRae, M. E.: Treatment of Scabies: Report of One Hundred Patients Treated with Hexachlorocyclohexane in a Vanishing Cream Base, J. A. M. A. **138**:557 (Oct. 23) 1948.

5. (*a*) Goldman, L.: Use of Repellents in Clinical Dermatology: General Principles, Arch. Dermat. & Syph. **60**:777 (Nov., pt. 1), 1949. (*b*) Recent Advances in the Chemical Control of Insects, Connecticut M. J. **13**:624, 1949.

6. (*a*) Templeton, H. J.: Personal communication to the author. (*b*) Lunsford, C. J.: Flea Problem in California, Arch. Dermat. & Syph. **60**:1184 (Dec.) 1949.

7. Goldman, L.: Lichen Urticatus Syndrome as a Manifestation of Sensitivity to Bites from Various Species of Arthropods, Arch. Dermat. & Syph. **58**:74 (July) 1948. Shaffer, B.; Spencer, M. C., and Blank, H.: Papular Urticaria: Its Response to Treatment with DDT and the Role of Insect Bites in Its Etiology, J. Invest. Dermat. **11**:293, 1948.

8. Dethier, V. G.: Chemical Insect Attractants and Repellents, Philadelphia, The Blakiston Company, 1947.

activities. Detailed studies of this type with various arthropods may help to determine why some cutaneous surfaces attract and others repel insects. Travis [9] indicated that there may be variations in repellent time in different individuals and in different species and that the time also varies with the mass population of the biting insects. In regard to determination of time of repellency, field tests are much less controlled than determinations of biting rates—of mosquitoes, for example—of known biting populations. In testing for repellency against chiggers it is difficult to differentiate between repellency and toxicant action. For the control of chiggers, the application of toxicant sprays to infested areas of ground is important.

There is of course no single mixture which is, as it were, universally and efficiently repellent against all arthropods of medical interest. The following are some repellents useful to the dermatologist:

1. Dimethyl phthalate—a good general repellent (may also be a miticide)
2. Rutgers 612—2-ethyl-1,3-hexanediol
3. 6:2:2 mixture—dimethyl phthalate, 60 per cent; 2-ethyl-1,3-hexanediol, 20 per cent, and indalone® (butyl ester of 3,4-dihydro-2,2-dimethyl-4-oxo-1,2-pyran-6-carboxylic acid) 20 per cent
4. NMRI-448—2-phenyl cyclohexanol and 2-cyclohexyl cyclohexanol
5. N-n-butylacetanilide—against fleas, ticks and chiggers
6. Dimethyl carbate (dimethyl ester of cis-bicyclo-[2,2,1]-5-heptene-2,3-di-carboxylic acid)—may be used alone or substituted for 2-ethyl-1,3-hexanediol in the 6:2:2 type combination
7. Tributyl phosphate—for fleas and ticks
8. N-n-amyl carbamide—for fleas and ticks
9. N-propyl-N,N-diethyl succinamate—for some species of Aedes and Simulium

From a clinical standpoint, both the vehicle and the active material must be considered in dermatology. The materials are incorporated usually in organic types of solvents, and the burning and the irritation from the use of them may be due to the vehicle rather than the repellent. In the use of 612 this solvent factor was disturbing to the troops in the field, and it is disturbing also in home use because of the action on varnish and paint. The use of these materials, then, about the eyes or the lips, on areas of acute sunburn and on irritated skin may be uncomfortable. Cream vehicles have been suggested by the Orlando, Fla., Laboratory of the Bureau of Entomology and Plant Quarantine. Percentages of liquid repellent in the cream may vary from 10 to 60 per cent; cold cream and vanishing cream types of bases are preferred although, surprisingly, paste vehicles, less easy to use, may provide greater protection than creams or undiluted vehicles. Plastic vehicles are now being considered for repellents.

9. Travis, B. V.: Mosquito Repellents, Am. Perfumer & Essential Oil Rev., August 1947.

Because of the fact that repellents are used over large areas of the body and are used repeatedly, one should, in order to avoid toxic reactions, use only those materials which are recommended as safe. Although these materials are in general substances of low sensitizing index, dermatitis has been observed from dimethyl phthalate and NMRI-448. Our experiences with N-n-butylacetanilide have been limited to some patch test studies which revealed no eczematous reactions. When combinations of repellents are proposed, the toxicologic and sensitizing studies must be repeated for the mixture. Toxicity of vehicles must always be considered.

The dermatologist should consider the property of attraction in terms of the humidity of the skin and the presence of a dermatitis with oozing and crusting which may attract insects. Topical medication used for the treatment of dermatologic lesions may also contain substances which may serve as attractants. This property of attraction has to be considered, then, in the occurrence of a dermatitis and its therapy, especially in subtropical or tropical areas. The study of physiology of the skin is again important here. The recent tendency to combine repellents with sun tan oils may not be successful at times because of attractant qualities of some of the materials in the mixture.

A review [10] of the recent developments in the field of toxicants illustrates how rapidly important developments are occurring. The search for newer and better compounds, originally stimulated by war requirements, has continued as the problems of economic entomology are realized in the settlement of the peace of the world. Meeting the problem of the future of the tropics, as regards economy, colonization and the like, depends to some extent on the practical developments in the field of repellents and toxicants.

Some toxicants now in modern use and, it is emphasized repeatedly, still under investigative study will be listed. This listing does not imply always recommendation for clinical usage. The large number of chlorinated hydrocarbons should be noted.

1. DDT—2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane
2. DDD—2,2-bis(*p*-chlorophenyl)-1,1-dichloroethane; TDE; rhothane® D-3

10. (*a*) Andrews, J. M., and Simmons, S. W.: Developments in the Use of the Newer Organic Insecticides of Public Health Importance, Am. J. Pub. Health **38**:613, 1948. (*b*) Knipling, E. F.: Newer Insecticides, Acarcides and Repellents for the Control of Arthropods Attacking Man, read before the Fourth International Congresses on Tropical Medicine and Malaria, Washington, D. C., May 1948. (*c*) Lehman, A. J.: The Toxicology of the Newer Insecticides, read before the Fourth International Congresses on Tropical Medicine and Malaria, Washington, D. C., May 1948. (*d*) Heyroth, F.: Personal communication to the author. (*e*) King, W. V.: Personal communication to the author. (*f*) Stage, H. H., and Bishop, F. C.: Equipment for Applying Insecticides, read before the Fourth International Congresses on Tropical Medicine and Malaria, Washington, D. C., May 1948.

3. Methoxychlor—2,2-bis(*p*-methoxyphenyl)-1,1,1-trichloroethane
4. Benzene hexachloride—1,2,3,4,5,6-hexachlorocyclohexane; GBH; 666; gammexane®; kwell® ointment
5. Toxaphene—chlorinated camphene, a mixture of several isomers; 3956; Hercules 3956
6. Chlordane—1,2,4,5,6,7,8,8-octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindane; 1068
7. Piperonyl derivatives—piperonyl cyclonene, piperonyl butoxide
8. MYL powder (Bushland)—pyrethrum, N-isobutyl undecylenamide, isopropyl cresols, 2,4-dinitro anisole and pyrophyllite
9. Pyrethrins
10. Parathion—0,0-diethyl-0,*p*-nitrophenyl thiophosphate; 3422; E-605
11. TEPP—tetraethyl pyrophosphate
12. HETP—Hexaethyl tetraphosphate
13. Phenyl cellosolve®—ethylene glycol monophenyl ether
14. Eurax®—crotonyl N-ethyl o-toluidide
15. Diphenyl carbonate
16. X,x'-dichloro-diphenyl ether
17. Octamethyl pyrophosphoramide
18. Thiocyanates—lethane® 384 (1-thiocyano-3,6-dioxadecane or B-butoxy-B-thiocyano diethyl ether); lethane® 384 special (a mixture of lethane® 384 and 2-thiocyanoethyl esters of C_{10} to C_{18} acids); lethane® 60 (2-thiocyanoethyl laureate)

When one considers the modern insecticide in relation to the skin one must know the exact formula of the mixture of the agent and the vehicle, the properties of all these materials and the exact method of use. Frequently the vehicle may be responsible for cutaneous irritation and even for systemic toxicity. Toxicants may be used generally in five ways:

1. In dust—talc, clays, pyrophyllites—1 to 2 per cent
2. In wettable powders—dispersal or solution in water—with surface-active agents
3. In emulsions
4. In solutions
5. In aerosols—generated by heat, mechanically or by liquefied gas—in use mainly as space sprays; no (?) residual toxicity
6. In creams

USES OF THE VARIOUS PREPARATIONS

DDT.—In recent periods DDT has been used extensively especially in malarial control surveys, especially in area control and in residue treatment of buildings. For the dermatologist there may be some interest in the fact that perhaps an efficient contact repellency may also be a property of DDT. The deficiencies of DDT as a toxicant seem to depend chiefly on a slower knockdown quality and ineffective-

ness against certain arthropods of dermatologic interest, especially ticks. There has been some study of the new analogs of DDT, especially the methoxychlor analog, now recommended for spraying of dairy cattle, and TDE or DDD. It would seem that both methoxychlor and TDE should be studied for use as dermatologic agents. Methoxychlor is now available for household use. There are disturbing reports of acquired resistance of flies and mosquitoes to DDT.

As yet, DDT, and not the analogs, has been used in practice, especially in the treatment of scabies and pediculosis. The details of therapy have been presented before. Some types of formulas which have been studied and are available follow:

1. NBIN (topocide®)—benzyl benzoate 68 per cent; ethyl *p*-aminobenzoate (benzocaine), 12 per cent; polysorbate 80, 14 per cent, and DDT, 6 per cent, by weight; this material is diluted with five times its volume of water
2. ENBIN—a similar type of formula
3. A cellulose cream of benzyl benzoate containing 1 per cent DDT (ungt,® gratavec®)

Because of the widespread use of DDT there is usually extensive contamination of the skin and some degree of ingestion and some degree of inhalation. DDT compounds are of course more dangerous to handle when in solution than when in wettable powders or dust forms. Repeated exposure of course increases the danger. It is curious that as yet there are no detailed visceral toxicologic studies on the stable emulsions and creams now used in dermatologic practice. The importance of the concentration of DDT in food and fodder, for example, has been detailed before. Fatalities have resulted chiefly by ingestion. In all claims of acute or chronic visceral toxicity detailed critical studies are necessary. If these were made there would be less hysterical clinical notes. In the reports of severe visceral reactions from skin contacts, the vehicle, especially if it is of the organic solvent type, must be considered. In simple terms, if DDT is used as it is recommended and not misused, it is safe.

DDT shows little cutaneous sensitizing reaction. The maculopapular eruptions detailed by Stryker and Godfrey [11] and the papulosquamous dermatitides reported by Gordon in West Africa have been suggested but not proved to be caused by DDT. Niedelman [12] reported a contact dermatitis with reactions also to the kerosene vehicle. Leider (cited by

11. Stryker, G. V., and Godfrey, B.: Dermatitis Resulting from Exposure to DDT, J. Missouri M. A. **43**:384, 1946.

12. Niedelman, M. L.: Contact Dermatitis Due to DDT, Occup. Med. **1**:391, 1946.

Higgins and Kindel [18]) reported a proved eczematous dermatitis. In our department, Higgins and Kindel [13] reported detailed studies of an exfoliative dermatitis produced by DDT. Repeated testing to DDT and its analogs is still being done. At the time of writing, the patient whose case was reported by Higgins and Kindel had long since recovered from his exfoliative dermatitis and had lost his eczematous hypersensitivity to DDT and to all the other analogs except the tribromoethane analog.

For the proved systemic reactions to DDT, chiefly by the nervous system, administration of barbiturates is recommended. Treatment with diphenylhydantoin (dilantin®) sodium, urethane and calcium gluconate has been mentioned.

MYL.—MYL has been used extensively in treatment of pediculosis in Mexico, and, since it contains an ovicide, it is also an effective control measure. This mixture was used in 1943 and 1944 and has been superseded in practice generally by DDT. As a rule MYL requires two applications, as for example in the control of pediculosis corporis.

Benzene Hexachloride.—Benzene hexachloride (hexachlorocyclohexane) is of interest to the dermatologist now because of the extensive use [4] of a 1 per cent concentration of the gamma isomer of 1, 2, 3, 4, 5, 6-hexachlorocyclohexane.

The impurities in the technical compound give it the musty odor which is disagreeable to some people. Deodorized material is used in clinical practice. This material is an effective scabieticidal agent, as was shown by work of Wooldridge [4a] and Cannon.[4b] Studies [10d] were being carried out at the time of writing to determine whether 0.5 per cent mixtures are as effective as 1 per cent mixtures. Recently a 1 per cent liquid preparation was made available.

A 1 per cent dust may be used for pediculosis capitis. This insecticide, also, is reported to be superior to DDT or DDD against the body louse.[13a] Also of dermatologic interest is its value against rodents. In impregnated cloth tests, King [10e] found hexachlorocyclohexane of value against fleas and ticks even after five months of indoor aging and after twenty launderings of the cloth in hot soapy water. Hexachlorocyclohexane penetrates the skin from impregnated cloth.

Hexachlorocyclohexane, then, passes readily through the skin. The systemic reactions in animals are chiefly those of the nervous system. One patient treated for an impetiginized scabies with an ointment containing benzene hexachloride manifested vertigo, headache and an excited stage after use of the salve for two days. It was later established that these reactions were due to an antihistaminic drug which

13. Higgins, E. L., and Kindel, D. J.: Dermatitis Exfoliativa from Exposure to DDT, J. Invest. Dermat. **12**:207, 1949.

13a. Andrews and Simmons,[10a] p. 621.

the patient was taking for the attempted relief of his pruritus. Due caution should be used in the prescription of antihistaminic preparations together with these toxicants. Mobbs [14] suggested but did not prove that the convulsive death of a child (and some animals) resulted from presumed contact with a dust containing hexachlorocyclohexane and also DDT and sulfur. No visceral toxicologic studies had been made at the time of writing on the actual creams and liquids containing hexachlorocyclohexane used in dermatologic practice. Following the suggestions of Heyroth [10d] we were using a 0.5 per cent concentration. In agreement with others we had observed no contact dermatitis from hexachlorocyclohexane. As with many of the chlorinated hydrocarbons, overexposure through absorption should always be watched for, since there may be no signs by skin irritation.

Chlordane.—Andrews and Simons [10a] stated that, "of the recently developed synthetic organic insecticides, chlordane is one of the more promising with respect to the control of some insects of public health importance." Our experience with this compound has been with the investigation of its patch test reaction both with and without vehicles. We have found chlordane substantially to be a compound of low sensitivity index. Because of the lack of sufficient toxicologic data it is not possible as yet to do extensive clinical studies in man with this excellent insecticide, although it has been used in sprays and emulsions in agricultural work. It appears to have a value against ticks and mites. In animals, chlordane affects chiefly the central nervous system. The dermatitis which may result from this commercial use would be suspected to be due more to the kerosene vehicle than to the material itself. Mixtures of chlordane and toxaphene are used in agriculture at times.

Toxaphene.—This preparation may be of interest to the dermatologist because of its effectiveness on bedbugs.[14a] For louse control, this compound is more resistant to laundering that DDT is. At present we have had no practical experience with it. It is reported to be very effective as dust and is of value in the area control of mites. This compound as yet has not been recommended as a household insecticide.

Piperoxyl Compounds.—These are used chiefly as pyrethrum synergists, for special value against the house fly and mosquito. The function of the synergist is that "combined with the insecticide it not only increases the initial effect of the insecticide by providing quicker knockdown and greater kill but often extends the duration of its residual effect." [10b] These compounds may also be used with DDT against DDT-resistant flies and mosquitoes. Pyrethrum has recently been synthesized,

14. Mobbs, R. A.: Toxicity of Hexachlorocyclohexane in Scabies, Correspondence, J. A. M. A. **138**:1253 (Dec. 25) 1948; Hexachlorocyclohexane in Scabies, Correspondence, ibid. **139**:1224 (April 23) 1949.

14a. Cited by Andrews and Simmons,[10a] p. 622.

and this synthetic product is reported to have a killing rate comparable with that of the natural product. As yet, we have done no skin tests with the synthetic esters of the type of the pyrethrins. This point is of interest to the dermatologists because pyrethrum is a good sensitizing agent.

Parathion.—Parathion, as well as the other organic phosphates, tetraethyl pyrophosphate and hexaethyl tetraphosphate, is toxic to all arthropods attacking man and animals and, incidentally, to man. Skin irritations have been reported from the use of parathion in agricultural work. Skin absorption may occur from impregnated cloth. Parathion may be absorbed in dangerous quantities without any dermatitis to warn the person of his overexposure. Animal experiments have shown severe parasympathetic nervous system stimulation, like muscarine poisoning. At the time of writing there had been three deaths from parathion, one presumably due to skin absorption and two to the inhalation of wettable dust or fumes.

Because of the importance of absorption through the skin, protection of the skin must be secured by the wearing of rubber gloves and even protective clothing. Goggles and a respirator are also necessary. The same general principles of protection apply here as in connection with the contamination of the skin through vesicant chemical warfare agents. Parathion is also under study as a rodenticide.

Ethylene Glycol Monophenyl Ether.—Ethylene glycol monophenyl ether is suggested for the treatment of pediculosis capitis. It is often used in a shampoo mixture. It has been tried in control programs for pediculosis, with ethylene glycol monophenyl ether used on the scalp and DDT mixtures used on the body.

Crotonyl N-Ethyl o-Toluidide.—After laboratory experiments by Domenjoz [15] on a critical study of acaracidal effects, this compound was developed in Switzerland [16] and has been used in the treatment of scabies. We have found this an effective scabicide with prompt relief of pruritus also. Reports on the value of this material in this country were given by Couperus,[17] Tronstein [18] in our department and Peck and Kierland (cited by Couperus [17]). It has been possible in Phthirus pubic infestation of the cilia to use this material directly on the cilia. In our experiments, we have observed no dermatitis and no suggestions of any toxic reactions. Studies of chronic toxicity are now under way.

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15. Domenjoz, R.: A New Scabies Remedy, Schweiz. med. Wchnschr. **76**:1210, 1946.

16. Burckhardt, W., and Rymarowicz, R.: Experiences with a New Scabies Remedy, "Eurax" (Geigy), Schweiz. med. Wchnschr. **76**:1213, 1946.

17. Couperus, M.: The Use of N-Ethyl-O-Crotono-Toluidide in the Treatment of Scabies and Various Pruritic Dermatoses, J. Invest. Dermat. **13**:35, 1949.

18. Tronstein, A. J.: (Ten Per Cent Crotonyl of Ethyl-O-Toluidine Ointment Eurax), a New Scabieticidal Agent, Ohio State M. J. **45**:889, 1949.

Miscellaneous.—The thiocyanates are reported [19] to cause moderate irritation of the skin. Among the miscellaneous insecticides that may be of interest to the dermatologist, especially in relation to pediculosis, are a mixture of *p*-chlorophenyl-chloromethyl sulfone and phenyl-chloromethyl sulfone, Lauseto neu of the Germans and the bisethyl xanthogen of the Russians. Some other scabicides which may be mentioned are benzyl salicylate, the methyl ester of phenoxyacetic acid, and tetraethylthiuram monosulfide. The Orlando Laboratory of the Bureau of Entomology and Plant Quarantine of the Department of Agriculture has tested over six thousand compounds as toxicants against chigger mites, and eighteen of the most promising for uniform impregnation were tested by Cross and Snyder (cited by King [1b]). The five favored were benzil, 2-thenyl benzoate, *p*-cresyl benzoate, diphenyl carbonate and 2-thenyl salicylate. At present octamethyl pyrophosphoramide has been used chiefly for the protection of plants.

Another technic of personal protection has been the impregnation of clothing by means of solutions of the toxicants. The process has been perfected so that a number of launderings may not succeed in removing all the impregnation into cloth. As has been emphasized before, cutaneous absorption can occur from impregnated cloth. In the laboratory 2 per cent acetone solutions may be applied to cloth, the cloth allowed to dry and then the tests against insects carried out. Such tests are excellent for the rapid screening of new compounds.

There were some interesting experiments done by Knipling, Bushland, Babers, Culpepper and Raun,[20] in relation to the effect on ectoparasites of orally ingested insecticides. These experiments were chiefly of investigative nature and limited to the rabbit, with the Pediculus humanus and other insects feeding on the rabbit. Such work is of considerable interest and promise for the future. In general, a material which was a good contact insecticide did not necessarily have good activity with regard to ectoparasites. The feeding of 2-pivalyl-1,3 indandione to the rabbit was toxic to pediculi feeding on the rabbit even several days after its ingestion of this particular agent. This material was highly effective against lice but was less effective against mosquitoes. However, when hexachlorocyclohexane was fed to the rabbits, it was less effective for pediculi and more effective for mosquitoes. Those experiments open up an entire new field in relation to a technic of protection of human beings. Here, of course, detailed knowledge of systemic toxicity is necessary. The same technic had been suggested in the use

19. Thieman, H. A.: New Insecticides and Rodenticides and Their Health Aspects, Indust. Hyg. Quart. **10**:10, 1949.

20. Knipling, E. F.; Bushland, R. C.; Babers, S. H.; Culpepper, G. H., and Raun, E. S.: Evaluation of Selected Insecticides and Drugs as Chemotherapeutic Agents Against External Blood Sucking Parasites, J. Parasitol. **34**:55, 1948.

of repellents. Attempts to control the degree of the bite reaction have been made by the oral use of thiamine hydrochloride. In addition, Lunsford [6b] and Templeton [6a] found thiamine hydrochloride of value as a repellent for fleas.[21] We agree with Wilson, Mathieson and Jachowski [22] that this material was not of any appreciable value in controlled studies on the effect of bites from mosquitoes and fleas. Antihistaminic drugs may show more promise in that regard. However, our preliminary experiments with biting by Aedes aegypti on normal skin and on skin with absorption of antihistamine drugs by iontophoresis showed no decided differences between the early and the late bite reactions.

The importance of detailed knowledge, then, of studies on acute and chronic toxicity is obvious. It is hoped that in spite of the highly competitive character of the commercial aspects of the chemical control of insects, the necessity for such studies will not be forgotten. It is well in this connection to emphasize the importance of the extensive toxicologic studies in this field done by Lehman [10c] of the Food and Drug Administration. For the present review, primarily for dermatologists, I have omitted discussion of many of these toxicologic studies on animals, plants and man.

There is a definite technic of progressive analysis of materials recommended for the chemical control of insects. First, it is obvious that a material must be effective either as a repellent or a toxicant, or as a combination, if possible. Determination of these properties lies in the field of the chemist and the entomologist. Toxicant qualities can often be determined by observation of the insect in contact with cloth impregnated with the toxicant. Then, animal toxicity studies, employing such means as the percutaneous absorption technic of Draize, Woodward and Calvery,[23] parenteral administration, feeding and dust inhalations, may be made. With the implications of the widespread use of such chemicals, certainly studies could be carried over a period of at least several years in order that the chronic phases of toxicity might be determined. Examples of such pertinent studies are those which were done by Lehman [10c] and by Kehoe [24] and his associates. Skin irritation tests on rabbits must be interpreted with caution if one desires to apply the results of these tests to man. If an estimate of the skin sensitizing index is desired, certainly skin of the guinea pig is preferred. However,

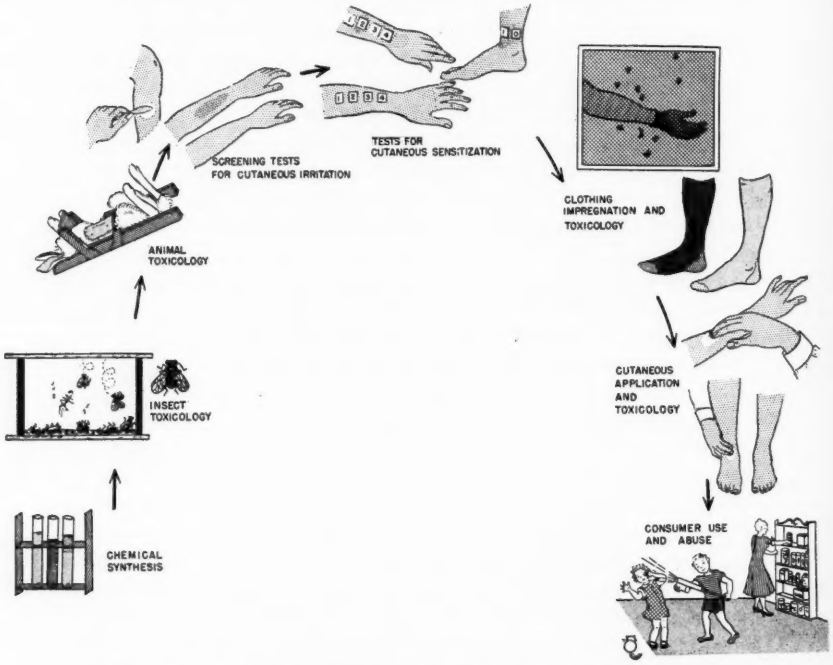
21. Shannon, W. R.: Thiamin Chloride—Aid in Solution of the Mosquito Problem, Minnesota Med. **26**:779, 1943. Eder, H. R.: Flea Bites—Prevention and Treatment with Thiamin, Arch. Pediat. **62**:300, 1945.

22. Wilson, C. S.; Mathieson, D. R., and Jachowski, L. A.: Ingested Thiamin Chloride as Mosquito Repellent, Science **100**:147, 1944.

23. Draize, J. H.; Woodward, G., and Calvery, H. D.: The Percutaneous Absorption of DDT in Laboratory Animals, J. Pharmacol. & Exper. Therap. **82**:159, 1944.

24. Kehoe, Robert A.: Personal communication to the author.

experiments on human skin must always be done. Rapid screening tests should be made on human skin to determine the quality of primary irritation, and controlled tests for primary irritation of the skin are certainly needed. The routine patch test technic, as has been emphasized repeatedly, is not a standardized technic for the testing of primary skin irritation: the covered heavy pad soaked with the material under study and the "controlled" rubbing tests on different areas of skin are some of the technics used. Later the detailed technics for determination of actual or potential eczematous sensitization are employed. These



Stages of development of insect repellents and toxicants, showing the importance of the dermatologic aspects as the material is used on man.

include the routine patch test with suitable types of vehicles. Then, for the attempted testing of potential sensitization, repetitive tests, such as repetitive patch testing after an interval of two weeks, as recommended by Schwartz, or the multiple repetitive technic, which we have been studying (repeated forty-eight hour applications to the individual site and then repetition of the forty-eight hour test in two weeks on this site and on untested skin), may be used. In addition, we have attempted to find promptly materials of low sensitizing index by patch testing of

actual areas and borders of the highly sensitizable skin of persons with the stasis syndrome, along with testing of controls. We have also used the skin of the upper eyelids. The Committee on Standardization of Cutaneous Testing of the Society for Investigative Dermatology is studying the important problem of the development of skin tests for the detection of potential eczematous sensitization, and also the elaboration of a controlled usage test.

After the aforementioned tests it is necessary to study reactions to the wearing of cloth impregnated with the substance so that relatively large areas of the body are exposed simultaneously in order to determine further local and systemic reactions. For this purpose subjects often wear impregnated socks or stockings. Finally, detailed field experiments under varying weather conditions will determine the practical value of the preparation as a repellent or toxicant and also its effect on the skin under those field conditions. With regard to repellents, control studies of similar areas of the body should be done and also control group types of studies may be done. Then, selected group or community usage tests may be made after the manner outlined by Schwartz and Peck. After all these controlled clinical experiments the work may be further carried out with children, and then a detailed review of the possible effects of these materials among civilians should be made before the material is recommended for general consumer use. One may note that if a substance is desired only for impregnation into cloth and not for direct application to the skin then under "certain special" circumstances a "somewhat irritant" material may be used, especially for military requirements where the need may justify it and where discipline can control reactions.

It is worth while for the dermatologist to consider any developments of laboratory technic which would contribute toward efforts to control the preliminary phases of the activity of the insect on the skin. The technic of Culpepper [25] of the rearing of body lice on rabbits and recently on white rats is certainly an important contribution in dealing with this problem. The technic of Domenjoz [15] for the laboratory study of the effect of chemicals on the motility of Psoroptes cuniculi, the scabies mite of rabbits, also provides a practical test for rapid evaluation of acaricides. Such technics have been applied clinically for some time by Mellanby [26] and by Eddy,[27] who made repeated and careful examinations of the numbers and activities of mites on the human skin after selected intervals after application of various acaricides. For this type of study we, too, have used the Greenough type binocular microscope

25. Culpepper, G. H.: Personal communication to the author.

26. Mellanby, K.: Personal communication to the author.

27. Eddy, G. W.: Preliminary Evaluations of Some New Synthetic Organic Compounds as Scabicides, J. Invest. Dermat. **12**:117, 1949.

on a long arm. As yet, use of the portable skin microscopes has not been effective in such control studies. At present studies employing cutaneous microscopy are under way on the detailed progress of the insect bite reaction.[28]

SUMMARY

The protection of the individual, with his living quarters and other parts of his environment, and chemical and laboratory research are important features of the modern program for the chemical control of insects. This program in all its phases is an important part of modern preventive dermatology and of global dermatology. Since many of the developments and their applications in the chemical control of insects involve cutaneous contact, absorption and penetration of substances employed against the insects, it is well for the dermatologist to be interested in all the collateral features of these programs. The necessity for studies of acute and chronic toxicity is shown. The entomologist, the toxicologist and the dermatologist must now work together in the development and use of new materials and in the control of use of some of the compounds now employed. The materials now recommended for repellency and toxicant action are of low sensitizing index. However, the features of acute and chronic systemic toxicity through skin absorption must still be considered, for the absence of warning dermatitis may lead to overexposure. Unfortunately, at times new materials are put into use without recommendations of proper agencies. Consequently many of these newer agents must still be considered investigative materials. The dermatologist must be alert to the dangers of these new materials and must be prepared to consider critically such factors as the compound itself, the vehicle and the technics of use and abuse. The materials finally available should be used only as recommended.

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ABSTRACT OF DISCUSSION

DR. THEODORE CORNBLEET, Chicago: This paper shows the growth of dermatology at all of its frontiers to meet with other interdependent disciplines. The chemist, entomologist, pharmacologist and dermatologist are shown to effectively pool their knowledge and experience in a common effort. Modern dermatology, contrary to what has been alleged, is seen to be not a narrow specialty but a constantly broadening one. Another thing pointed up in Dr. Goldman's presentation is the great care and patience necessary in preparation of a new product for the market. Those of experience know the great danger that lurks in taking short cuts from the laboratory to the advertiser without due clinical trial.

28. Gordon, R. M., and Crewe, W.: The Mechanisms by Which Mosquitoes and Tsetse-Flies Obtain Their Blood Meal, the Histology of the Lesions Produced, and the Subsequent Reactions of the Mammalian Host, Together with Some Observations on the Feeding of Chrysops and Cimex, Ann. Trop. Med. **42**:334, 1948.

Dr. Goldman has adequately stressed the importance of the person himself, his secretions, emanations and capacities for irritation and sensitization as a highway for or barrier against insects. We need by all means to press our search for efficient and safe insecticides, but we have also to intensify our efforts to learn what makes people immune or susceptible to attack. Thus, pediculosis corporis is largely a disease of the underprivileged, a class that shows evidence that the critical factor for infestation is a lack of sufficient riboflavin.

Hexachlorocyclohexane can induce cytogenetic changes and atypical growth in various types of seedlings. It has a colchicine-like action. There is cause enough to make one wonder whether the absorption of this or other insecticides could occur in sufficient amounts to become injurious to the young fetus of a pregnant woman. Investigation in this direction would seem to be desirable, first, of course, in laboratory animals.

We can borrow some ideas from the plant world in the fight against insects. The first is to intervene in the ecology of the insects when our chemical weapons alone are not efficient enough. In certain instances insects and birds have been newly introduced or imported to prey on the destructive varieties. Perhaps the entomologist could help us extend this practice to our domain.

Secondly, where plants have been especially vulnerable to disease or insect attack, breeders have learned to develop more resistant varieties. We cannot intervene readily in shaping the heredity of human beings, but we can fortify them against insects by other actions. There is evidence to show that the administration of thiamine hydrochloride makes a person less attractive to some insects. The question occurs, too, whether it is mere accident that insects are most troublesome where protein is likely to be in short rations and carbohydrates abundant.

Dr. Bertram Shaffer, Philadelphia: Since the summer of 1946 Drs. Malcolm C. Spencer and Harvey Blank and I have been treating papular urticaria with DDT. We have the patient apply a 5 per cent mixture of DDT in talc to his body several times a day. He also sprays his quarters with flit® containing 5 per cent DDT. We have been greatly impressed by the efficacy of this method of treatment. We have examined 87 patients with papular urticaria. When they were questioned carefully, it was found that 26 had known exposures to fleas, 8 had known exposures to bedbugs and 72 were exposed to sources of fleas, namely cats and dogs and accumulation of sand and other material of that sort.

Fifty-four of these patients were treated with our DDT regimen. Of these, 86 per cent experienced cure within two weeks. By "cure" I mean that their itching stopped completely and no new lesions appeared. Only 2 persons in our group failed to show any improvement.

We reviewed 88 cases of papular urticaria in which there had been treatment by other methods in the previous ten years as a control group. In only 22 per cent was a cure listed, and the period for cure was eleven weeks. Obviously, papular urticaria having a seasonal incidence, many of the patients got well spontaneously.

Extracts were made of bedbugs and fleas and used for intracutaneous tests, the reactions to which were read in forty-eight hours. Of 30 patients thus tested, 77 per cent showed positive reactions to the injection of fleas and/or bedbugs. In a control group of 124 patients of about the same race and age group, only 2 showed positive reactions. My associates and I feel that we have good evidence to indicate that papular urticaria frequently results from a reaction to the bites of fleas and bedbugs.

Dr. Leon Goldman, Cincinnati: I believe most of these cases of lichen urticatus, especially those not in atopic persons, are due to allergic reactions to bites of insects. These insects may not necessarily be only the fleas and bedbugs. Kenneth Mellanby

expressed the belief that most of the cutaneous reaction of scabies is that of the sensitivity reaction, especially as the disease progresses, and that in the average case of well developed scabies, as a rule, there are only about twelve female parasites. I think it has been shown by carefully controlled experiments by entomologists that thiamine hydrochloride has no true value as a repellent when taken orally.

Of the isomers of hexachlorocyclohexane only the gamma isomer has any appreciable insecticidal quality, and it is the most toxic against human beings. That is the current rule that follows the development of an insecticide: if it is toxic against insects, it is also toxic against man. Curiously, I cannot find any evidence at present of any detailed toxicologic studies that have been done on our favorite preparations of DDT and benzyl benzoate and the gamma isomer of hexachlorocyclohexane in the vehicles employed, and yet these mixtures are used, and used abundantly, and they are "apparently" safe.

STREPTOMYCIN TREATMENT OF GRANULOMA INGUINALE

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DURING the period from November 1947 to June 1949, we had the opportunity to follow 76 patients having granuloma inguinale treated with streptomycin.[1] Over 60 per cent of these persons were observed for periods longer than six months after the initial course of streptomycin was administered. Therefore, this report offers significant information concerning the results of treatment.

It is not the purpose of this paper to review the literature on this subject, since this has been adequately done by several authors.[2] Moreover, it is beyond the scope of this presentation to describe the various clinical manifestations of the disease, since this aspect also has been adequately covered.[3]

The following criteria were used for inclusion of cases in this study: 1. Clinical diagnosis was accepted only if intracellular Donovan bodies were identified from material obtained from scraping. 2. All other venereal diseases were treated adequately before therapy for granuloma inguinale was instituted. In these circumstances, no healing of granuloma inguinale lesions was noted.

Since other criteria (complement fixation tests, skin tests and pathologic examinations) do not permit more than presumptive evidence of diagnosis, these methods of examination were not utilized except in a confirmatory manner.

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1. All patients were hospitalized at the Hampton Roads Medical Center, Norfolk, Va., by cooperation of the Virginia State Department of Health with local health departments throughout the state.

2. (*a*) Kupperman, H. S.; Greenblatt, R. B., and Dienst, R. B.: Streptomycin in the Therapy of Granuloma Inguinale, J. A. M. A. **136**:84 (Jan. 10) 1948. (*b*) Marshak, L. C., and Rodriquez, J.: Granuloma Inguinale, J. A. M. A. **137**:1292 (Aug. 7) 1948. (*c*) Pariser, H., and Beerman, H.: Granuloma Inguinale, Am. J. M. Sc. **208**:547 (Oct.) 1944.

3. (*a*) Pariser and Beerman.[2c] (*b*) Chen, C.; Greenblatt, R. B., and Dienst, R. B.: Recent Observations on Granuloma Inguinale, with Report on Streptomycin Therapy, Arch. Dermat. & Syph. **58**:708 (Dec.) 1948.

The treatment schedule was determined partially by trial and error but primarily as the result of the work of Greenblatt and his co-workers,[2a] who noted that their best results were obtained by employment of a schedule consisting of the intramuscular administration of approximately 4 Gm. of streptomycin daily for a period of five days in divided doses of 0.67 Gm. every four hours around the clock for a total dose of 20 Gm. Our limited experience with smaller dose schedules on a daily basis (0.5 to 2 Gm. per day) confirms the observation of Chen, Greenblatt and Dienst,[3b] that dosages approximating the aforementioned schedule offer better therapeutic results than do smaller dose schedules. In our series, all patients received 3.6 Gm. of streptomycin per day for a total of 18 Gm. over a period of five days in individual doses of 0.6 Gm. given every four hours around the clock.

Analysis of our cases failed to reveal any relation between response to treatment and extensiveness or duration of the disease, nor was there any difference in response to treatment according to analysis by sex, age or previous treatment with other drugs (antimonials), whether given in adequate or inadequate doses. The actual figures of these analyses are omitted, since they offer no clue to prognosis or potential response to treatment.

Since there are no absolute criteria of cure, relapse or reinfection and since granuloma inguinale is a disease notoriously prone to recur, we have arbitrarily regarded the following occurrences as indications for re-treatment after the first course of streptomycin: (1) Presence of intracellular Donovan bodies taken from smears of lesions several days or longer after the five day course of streptomycin treatment was completed. In such instances lesions failed to heal or, after partial healing (less than 30 per cent) extension took place. (2) Reappearance after complete healing of lesions from which Donovan bodies could be demonstrated intracellularly. Cases of this sort may conceivably have been instances of reinfection. Greenblatt [4] stated that in his experience all relapses occurred within a six month period after treatment. In this second category there were 4 cases, with reappearance of lesions at 5 months in 2 instances, at 11 months in 1 instance and at 3 and 16 months in 1 instance.

There were 88 patients treated in this study. Since 12 were lost to followup, their cases are not reported here. Of the remaining 76, 61 responded to one course of streptomycin. Twelve persons were re-treated on the basis of the first criterion and 3 on the basis of the second. All patients re-treated were given 4 Gm. of streptomycin daily for a period of ten days in doses of 0.67 Gm. every four hours around the clock.

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4. Greenblatt, R. B.; Dienst, R. B.; Chen, C., and West, R.: Oral Aureomycin in the Therapy of Streptomycin Resistant Granuloma Inguinale, South. M. J. **41**:1121 (Dec.) 1948.

Three patients failed to respond to this second course. One of these was given a third course of streptomycin consisting of 4 Gm. daily for a total of ten days, followed by a course of aureomycin consisting of the oral administration of 250 mg. every six hours, for a total of 1 Gm. a day for eight days. There was only partial healing under this regimen, and Donovan bodies persisted in the lesion. The patient was then placed on intensive treatment with stibophen (fuadin®) over a period of two months, during which time 245 cc. of the drug was administered intramuscularly in doses of 3 to 5 cc. daily to the point of toxicity (arthralgia). The lesion completely healed, only to recur after one month. Surgical excision is contemplated in this case. The second patient whose lesions failed to respond to a second course of streptomycin showed complete healing following the oral administration of aureomycin in doses of 250 mg. every three hours for a total of 2 Gm. a day for eight days. There was no recurrence of this lesion one month after treatment. The third patient with recurrent lesions after the second course of streptomycin was placed under treatment with chloramphenicol (chloromycetin®) consisting of the administration of 2 Gm. daily for nine days. Treatment has been carried out too recently for therapy to be evaluated in these 3 cases.

No significant toxic reactions were noted in any of the patients treated. Practically all patients complained of pain at the site of injection whether or not procaine was administered. About two-thirds of the patients showed a febrile reaction, with temperatures up to 100 F., for several days during treatment. A few acquired urticaria and toxic erythema, which in no instance required discontinuance of treatment.

The periods of observation after the administration of streptomycin were as follows:

Time Observed After First Course	No. of Cases
1 mo.	4
2-6 mo.	21
7-12 mo.	22
12-20 mo.	29
Total	76

Time Observed After Second Course	No. of Cases
0 mo.	2
1 mo.	2
2-6 mo.	6
7-11 mo.	2
12-19 mo.	3
Total	15

CONCLUSIONS

The lesions of 80 per cent of our patients with granuloma inguinale healed under treatment with a schedule of 18 Gm. of streptomycin given in divided doses of 0.6 Gm. every four hours over a five day period.

Treatment failures could be reduced to approximately 4 per cent by re-treatment with a dosage of 4 Gm. per day over a period of ten days.

Although the oral use of aureomycin and chloramphenicol may cause healing of lesions resistant to intensive therapy with streptomycin, our experience with these drugs is too limited for us to draw any conclusions.

EFFECT OF YEAST EXTRACT ON MICROSPORUM AUDOUINI AND MICROSPORUM CANIS

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CONANT,[1] in 1936, found that the use of polished rice medium assisted in the differentiation of Microsporum audouini from Microsporum canis. The former failed to grow abundantly on rice, producing only a progressive discoloration of the grains, while the latter grew luxuriantly. In 1943, Benedek [2] discovered that the presence of a certain bacterium on rice medium stimulated not only the growth of M. audouini but also the development of macroconidia characteristic of the genus Microsporum. The bacterium was studied, described and classified by the author as Bacillus weidmaniensis. In 1947, Hazen [3] found that the effects obtained by Benedek could be reproduced when M. audouini was grown on honey agar enriched by yeast. She expressed the opinion that M. audouini is deficient in certain factors which apparently are supplied by yeast extract. This opinion was also expressed by Benham.[4]

Luxuriant cultural growth on rice and formation of abundant spindle-shaped macroconidia on artificial mediums are two of the foremost characteristics of M. canis. By alterations of the mediums Benedek and also Hazen apparently succeeded in giving rise to a phase of growth resembling that of M. canis in colonies of M. audouini. Since this phenomenon is of both theoretic and practical significance I subjected it to further study. In this paper are reported data obtained from the observation of several strains of M. audouini and M. canis grown on various mediums, both plain and enriched with yeast extract.

From the Long Island College Hospital and the Department of Dermatology and Syphilology, Long Island College of Medicine, Brooklyn.

1. Conant, N. F.: Studies in the Genus Microsporum: I. Cultural Studies, Arch. Dermat. & Syph. **33**:665 (April) 1936.

2. Benedek, T.: Unilateral Stimulation of Microsporum Audouini by a New Species of Bacillus, Mycologia **35**:222, 1943.

3. Hazen, E. L.: Microsporum Audouini: The Effect of Yeast Extract, Thiamine, Pyridoxine and Bacillus Weidmaniensis on the Colony Characteristics of Macroconidia Formation, Mycologia **39**:200, 1947.

4. Benham, R. W.: Effect of Nutrition on Growth and Morphology of the Dermatophytes: I. Development of Macroconidia in Trichophyton Rubrum, Mycologia **40**:232, 1948.

MATERIALS AND METHODS

M. Audouini.—Both stock cultures and freshly isolated strains of M. audouini were employed. The stock colonies were derived from a strain of M. audouini, called strain C, which had been observed for 357 days.[5] Fuseaux had been observed in a small proportion only of the examinations of the mother colony and were never seen in the subcolonies. The colonies C.15,[6] C.1.1 and C.15.1 were used in this study. Viability of the colonies was determined prior to the actual experiments by transplantations on dextrose-peptone agar and rice medium. They grew on the former as yellowish brown mats with radiating furrows and developed only a slowly progressing discoloration on the grains of the latter. No fuseaux were observed on either medium. The freshly isolated strains of M. audouini were obtained from the scalps of 3 young girls with tinea. The clinical manifestations were those commonly seen in anthropophilic infection, namely, gray patches lacking signs of inflammation and having relative resistance to topical therapy. All the strains grew slowly on dextrose-peptone agar, developing a flat, somewhat grooved mat with brown pigment on the subsurface. Mounted culture slides did not show macroconidia of the fuseaux type.

M. Canis.—Cultures of M. canis were obtained from stock preparations and were also freshly isolated. The stock colonies were derived from a strain, called A, which had shown a remarkable degree of variability.[5] Fuseaux had been consistently absent from the mother colony and abundantly present in most of the subcolonies. Three colonies were selected and identified as A.22, A.23 and A.24. Fuseaux were sparse in the first and abundant in the second; A.24 had developed these structures on rice but not on dextrose-peptone agar. Three freshly isolated strains were obtained from three scalps with tinea of the inflammatory type. These strains grew rapidly on dextrose-peptone agar, developing an aerial mycelium and a canary yellow pigment. Mounted culture slides revealed many fuseaux.

Mediums.—The following mediums were used:

1. Dextrose-peptone agar (Difco). This contained 10 Gm. of neopeptone (Difco), 40 Gm. of bacto-dextrose and 15 Gm. of bacto-agar per liter.

2. Honey agar.[3] This contained 10 Gm. of neopeptone (Difco), 60 Gm. of commercial honey and 20 Gm. of bacto-agar per liter.

3. Polished rice.[1] To prepare this medium 20 Gm. of rice and 60 cc. of water were placed in a 125 cc. flask and sterilized for fifteen minutes at 15 pounds (7 Kg.) of pressure and 250 F. (121 C.).

The agar mediums were slanted in test tubes of 1 inch (2.5 cm.) diameter. All the mediums were used as indicated heretofore and enriched with bacto-yeast extract (Difco).[3] Five Gm. of the extract was dissolved in 100 cc. of distilled sterile water and was sterilized by passage through a Seitz filter. One part of the filtrate was added to 9 parts of the medium in order to produce in the latter a concentration of 0.5 per cent yeast extract.

The inoculated mediums were kept at room temperature and observed at weekly intervals for at least three weeks. Special attention was paid to the formation of fuseaux.

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5. Loewenthal, K.: Fuseaux Formation of the Genus Microsporum, Arch. Dermat. & Syph. **61**:455 (March) 1950.

6. First generation subcultures were designated by using the letter for the parent strain, C, separated by a period from a numeral which indicated the chronologic order of these primary subcultures, e. g., C.1, C.2 and so forth. Second generation subcultures were denoted by addition of another numeral separated from the first by a period, e. g., C.1.3 and so forth.

RESULTS

M. Audouini.—Yeast extract enrichment of the three mediums caused darkening and increase in the quantity of pigment. Mycelial changes also occurred, in the form of white aerial filaments on rice and a heavier matted growth on dextrose-peptone and honey agar mediums. Fuseaux were not observed on any medium, plain or enriched.

M. Canis.—Enrichment produced changes which differed in the freshly isolated and stock strains. The effect of yeast extract on the former, when rice was used as the medium, was to convert a sparse delicate mycelium into an abundant fluffy mat; when honey agar was employed there was an increase in the quantity and darkening of the pigment. Fuseaux were abundant on both plain and enriched mediums. Dextrose-peptone agar was not used for these strains.

The effect of yeast extract on stock colonies of strain A was observed on honey agar and rice mediums. With the former enriched medium a more luxuriant mycelium was obtained and a more copious and darker pigmentation produced; in the case of enriched rice the sole macroscopic change observed was a slightly increased rate of growth of A.22. The effect on fuseaux production varied in the different strains and with the mediums used. In the case of honey agar, in A.22 a sparse yield was replaced by an absence of these structures following enrichment, in A.23 there was no change in an abundant production of fuseaux and in A.24 no fuseaux were present either before or after enrichment. When rice was employed as the medium, the addition of yeast extract did not produce any demonstrable change in the same three strains.

COMMENT

A previous investigation dealing with the effect of enriched honey agar on M. audouini was repeated and extended to M. canis; besides honey agar, dextrose-peptone agar and polished rice were used. Stock cultures with known properties and, simultaneously, freshly isolated strains were employed.

Addition of yeast extract to any of the mediums produced the following changes in the gross appearance of the colonies of M. audouini and M. canis: increase in the rate of growth, appearance of or increase in the amount of aerial mycelium and an intensification of pigmentation. Enhanced rate of growth and increased production of aerial mycelium were observed primarily on rice; increase in aerial mycelium and intensification of pigment were most noticeable on the agar media. The faculty of fuseaux production, however, remained uninfluenced in the colonies of M. audouini and M. canis.

The results of this study are in agreement with Hazen's report of an increased growth of M. audouini on enriched honey agar; they are,

however, at variance with her microscopic observations, since the observation of increased production of macroconidia could not be substantiated, even on the extended experimental scale of this study. Furthermore, yeast extract did promote growth and pigmentation not only of M. audouini but also of M. canis without detectably influencing the fuseaux production of the latter. Further investigation, therefore, would be required before the suggestions of Hazen and of Benham, that M. audouini is an organism deficient in certain factors, could be accepted.

SUMMARY

Three freshly isolated strains and three stock colonies of M. audouini and also of M. canis were studied on various mediums, plain and enriched with yeast extract. Yeast extract stimulated the growth of the fungus colonies and intensified their pigment production; contrary to the reports of Hazen and of Benham, increased formation of fuseaux was not observed.

CHEMOSURGICAL TREATMENT OF MELANOMA

A Microscopically Controlled Method of Excision

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IN THE treatment of epithelioma the "silent" extensions from the main mass of cancer can accurately be followed out and eradicated by means of the multiple, microscopically controlled excisions which characterize the chemosurgical method.[1] In the treatment of melanoma, however, this microscopic control would seem to be of more limited value because often there is a discontinuous, embolic mode of spread into the peritumoral lymphatics and beyond. The purpose of this article is to attempt to clarify the place of chemosurgery in the treatment of this highly malignant disease through the analysis of a consecutive series of 20 cases of melanoma in patients who have been observed for five or more years or until death.

TECHNIC

The microscopic control of excision, which is the most important feature of the chemosurgical method, is attained by a process which includes (1) chemical fixation, in situ, of the tissue suspected of being cancerous by means of a paste containing zinc chloride,[2] (2) excision of a layer of the fixed tissue, (3) location of the cancerous areas by systematic microscopic examination of frozen sections of the excised tissues, (4) further chemical treatment limited to the areas demonstrated to be cancerous and (5) repetition of the process until the neoplasm, including all its irregular extensions, has been entirely excised. Inasmuch as the fixative is not reapplied to areas which are found to be free of cancer, the technic makes possible, in effect, the selective destruction of cancer tissue although the

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From the Chemosurgery Clinic, Department of Surgery, Wisconsin General Hospital, and the McArdle Memorial Laboratory, University of Wisconsin Medical School.

1. (*a*) Mohs, F. E., and Guyer, M. F.: Pre-Excisional Fixation of Tissues in the Treatment of Cancer in Rats, Cancer Research **1**:49 (Jan.) 1941. (*b*) Mohs, F. E.: Chemosurgery: A Microscopically Controlled Method of Cancer Excision, Arch. Surg. **42**:279 (Feb.) 1941.

2. The zinc chloride fixative contains 40 Gm. of stibnite (80 mesh sieve), 10 Gm. of powdered sanguinaria and 34.5 cc. of a saturated solution of zinc chloride.

fixative chemical itself has no selective cancerocidal effect. For the details of the technic, especially as related to tumors in specific sites, the reader is referred to several published articles.[3]

In the chemosurgical treatment of melanoma the same technic as is employed in the treatment of epithelioma is used, with one notable exception: instead of discontinuing treatment when a melanoma-free level is reached, one continues it until a zone of tissue well beyond the level at which melanoma is no longer microscopically demonstrated has been removed. The purpose of the removal of this extra tissue is to eliminate the possible outlying foci of melanoma in the surrounding lymphatics. The amount of extra tissue removed is dependent on two factors: the size of the neoplasm and the degree of malignancy. Thus, if the lesion is only 1 or 2 cm. in diameter and microscopic examination reveals a melanoma with only a moderate degree of malignancy, it is considered safe to remove as little as 1 cm. of tissue beyond the melanoma-free plane. On the other hand, if the melanoma is large and there is microscopic evidence of high malignancy it is advisable to remove more tissue, possibly several centimeters.

In the chemosurgical treatment of melanoma, great care is exercised to avoid rough handling of the tissues. During excision of the fixed tissues an extremely sharp scalpel is employed and care is used not to cut into unfixed tissue.

If the regional nodes are enlarged, surgical dissection is indicated unless there is massive fixation or inaccessible metastasis. In the absence of enlargement, prophylactic surgical dissection of regional lymph nodes may be advised if the primary lesion is larger than 1 or 2 cm. and microscopic examination shows evidence of invasion of vessel walls and pronounced anaplasia. If the lesion is small and the microscopic appearance of the tissue indicates a relatively low degree of malignancy it may be justifiable to remove only the primary lesion and then closely observe the regional nodes for a minimum of five years.

If there are nodules of grossly visible melanoma in the lymphatics at a considerable distance from the primary lesion a radical surgical excision of the primary lesion, the regional nodes and the intervening lymphatics in one block may be indicated rather than chemosurgical treatment. In some cases of melanoma affecting an extremity, amputation of the limb may be necessary. The technic of such procedures was well described by Pack and his associates.[4] In the present series

3. Mohs, F. E.: Chemosurgical Treatment of Cancer of the Lip: A Microscopically Controlled Method of Excision, Arch. Surg. **48**:478 (June) 1944; Chemosurgical Treatment of Cancer of the Nose: A Microscopically Controlled Method, ibid. **53**:327 (Sept.) 1946; Chemosurgical Treatment of Cancer of the Ear: A Microscopically Controlled Method of Excision, Surgery **21**:605 (May) 1947; Chemosurgical Treatment of Cancer of the Eyelid: A Microscopically Controlled Method of Excision, Arch. Ophth. **39**:43 (Jan.) 1948; Chemosurgical Treatment of Cancer of the Face: A Microscopically Controlled Method of Excision, Arch. Dermat. & Syph. **56**:143 (Aug.) 1947; Chemosurgical Treatment of the Extremities and Trunk: A Microscopically Controlled Method of Excision, Arch. Surg. **56**:818 (Dec.) 1948; Chemosurgical Excision of Cancer of the Skin: A Microscopically Controlled Method of Excision, J. A. M. A. **138**:564 (Oct. 23) 1948; Chemosurgical Treatment of Tumors of the Parotid Gland: A Microscopically Controlled Method of Excision, Ann. Surg. **129**:381 (March) 1949; The Preparation of Frozen Sections for Use in the Chemosurgical Technic for the Microscopically Controlled Excision of Cancer, J. Lab. & Clin. Med. **23**:392 (March) 1948.

4. Pack, G. T.; Perzik, S. L., and Scharnagel, I. M.: The Treatment of Malignant Melanoma—Report of 862 Cases, California Med. **66**:283 (May) 1947.

there was only 1 case in which there were deposits in the lymphatic vessels at a distance from the primary lesion; in this instance the primary lesion was on the lower portion of the leg and the nodule in the lymphatic was at the midthigh level. Owing to the essentially hopeless prognosis as a result of extensive involvement of the inguinal nodes, it was deemed inadvisable to sacrifice the leg. Accordingly, the primary and secondary foci in the leg were chemosurgically removed, and the inguinal nodes were resected by a member of the surgical staff. The leg lesions healed, and there were no new foci on the extremity when the patient died of inguinal and internal metastases after fourteen months. There may be encountered situations in which chemosurgical removal of the primary lesion might advantageously be combined with surgical removal of the lymphatics and regional lymph nodes.

END RESULTS AFTER FIVE OR MORE YEARS IN CASES OF CUTANEOUS MELANOMA

Twenty adult patients with microscopically proved melanoma were chemosurgically treated during a seven year period ending May 2, 1944, which date was over five years prior to this writing. The primary lesions varied widely in size, but ten of them were more than 3 cm. in diameter. Moreover, in 10 of the cases there was palpable enlargement of the regional lymph nodes. Twelve of the patients had received previous surgical or radiation treatment.

Of the 20 patients in this series 7 (35 per cent) had been living and well for five years or more after treatment. The patient who had remained well the longest had shown no evidence of melanoma after more than twelve years (fig. 1).

The causes of failure in the 13 cases in which treatment was unsuccessful were uncontrolled metastasis in 9 patients, coronary thrombosis during the treatment of recurrent melanoma of the conjunctiva in 1 patient and death of indefinite causes before the elapse of five years in 3 patients. The last group is included in the "unsuccessfully treated" category because the "stroke" in 1 patient, the "pneumonia" in another and the "undetermined cause of death" in the third all may have been due to melanomatous deposits.

Factors with Influence on Prognosis.—The factors which affected prognosis in this series were (1) the size of the primary lesion, (2) the degree of malignancy and (3) regional lymphadenopathy.

It would be expected that results would be better in cases in which the lesions were small. In this series there were 10 patients with lesions under 3 cm. in diameter, and 4 of these had cures, while in the 10 patients with lesions over 3 cm. there were three cures. The poor prognosis associated with larger lesions is of course largely due to the greater incidence of metastasis in such cases, but it is significant that even larger lesions can be cured in some instances.

Although there is no well defined classification of the degree of malignancy of melanoma there are certain microscopic criteria by which

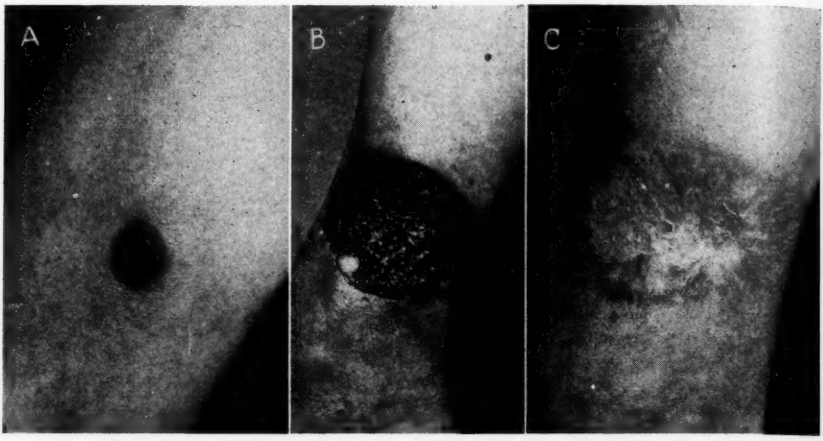

Fig. 1.—*A*, melanoma on tibial crest, recurrent after treatment with radium. *B*, granulation tissue after the second chemosurgical removal. The first removal had been inadequate because satellite skin nodules had appeared. *C*, healed lesion. An inguinal node the size of a small walnut appeared in the groin, and block resection of the node-bearing tissues by Dr. E. R. Schmidt revealed only this one metastatic deposit. The patient had shown no evidence of melanoma after twelve years.

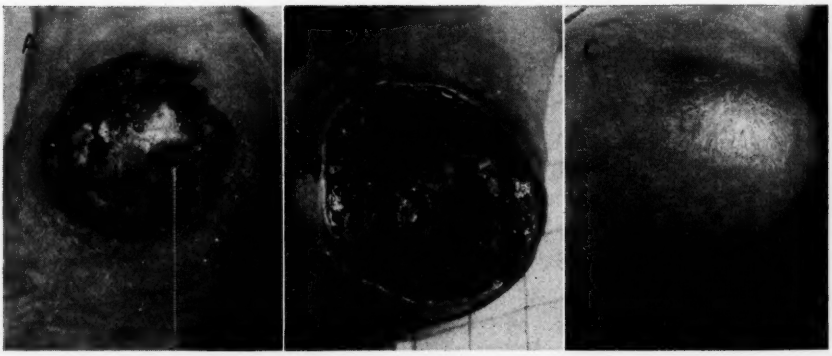

Fig. 2.—*A*, melanoma on heel recurrent after treatment with caustics, electrosurgical excision and roentgen ray. The inguinal nodes were enlarged but on resection showed inflammatory rather than metastatic involvement. *B*, granulation tissue after chemosurgical removal of the melanoma plus at least a centimeter of extra tissue at the periphery. *C*, healed lesion. The soft pliable scar was not uncomfortable on walking. There had been no evidence of melanoma after eight years.

the prognosis may be estimated. Chief among these are the invasion of vessel walls and the degree of anaplasia (fig. 5). In addition, it was observed that pigmented melanomas had a better prognosis than those

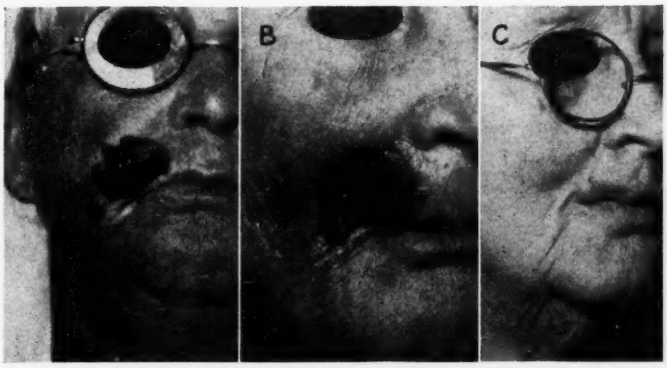

Fig. 3.—*A*, melanoma arising in the medial half of a junctional nevus. The neoplasm had recurred after electrodesiccation. *B*, granulation tissue after chemosurgical excision of the melanoma, the nevus and an extra zone of 5 to 10 mm. at the periphery. *C*, healed lesion. There had been no evidence of melanoma after six years.

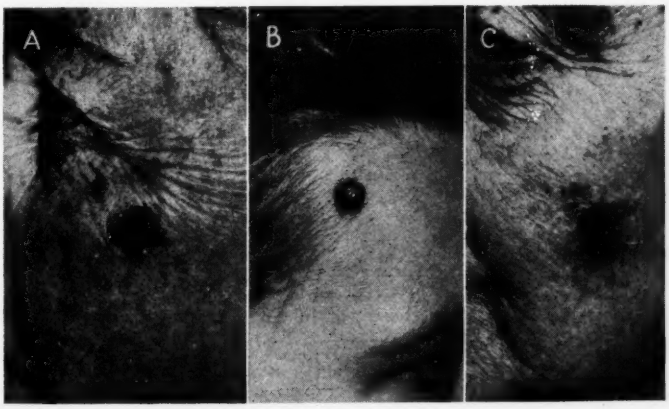

Fig. 4.—Lesions resembling melanoma clinically. These lesions were very conservatively removed with the chemosurgical technic with correspondingly excellent cosmetic results. *A*, granuloma pyogenicum. *B*, hemangioma which had arisen and grown rapidly during pregnancy. The surface was black as a result of silver nitrate applications. *C*, seborrheic keratosis which had grown rapidly and was heavily pigmented.

without pigment. Also, the presence of hemorrhage in the neoplasm was of unfavorable prognostic import.

By the consideration of the invasion of the vessel walls, the degree of anaplasia, the pigmentation and the hemorrhagic tendency exhibited by a given melanoma, the degree of malignancy and hence the prognosis can be fairly accurately predicted. Thus, there were no successful results in the group of eight melanomas in which three or four of these factors were listed as unfavorable. There was only one favorable result in a group of 3 cases in which two unfavorable factors were present. On the other hand, when no unfavorable factor or only one was present, successful results were attained in 6 of 8 cases (75 per cent).

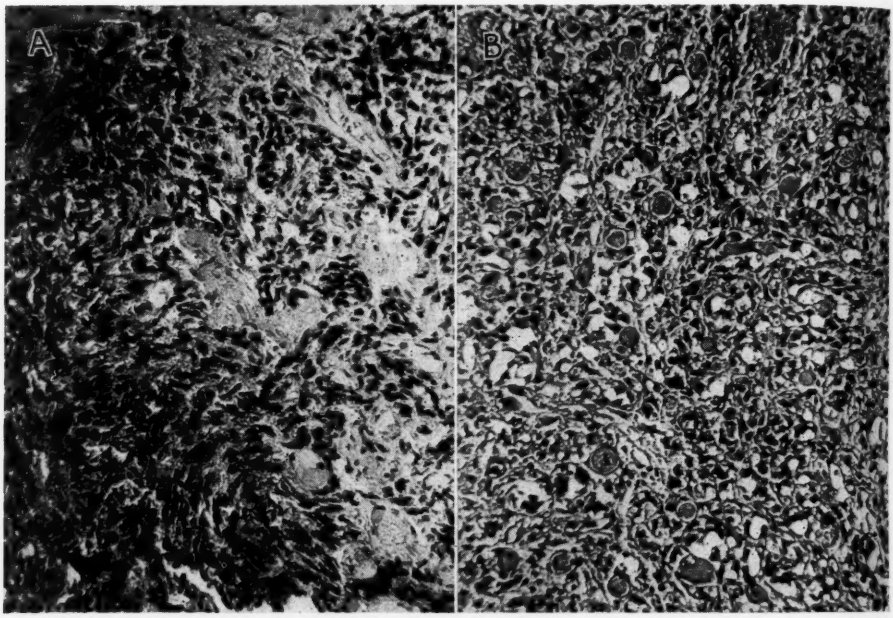

Fig. 5.—Photomicrographs showing two melanomas with different degrees of malignancy and with correspondingly different outcome of the cases. *A*, melanoma with a high degree of anaplasia and with invasion of the thin-walled vessels. The patient died of axillary and internal metastases though the primary lesion did not recur. *B*, melanoma with only moderate anaplasia and with intact vessel walls. The patient showed no evidence of melanoma after six years.

The most crucial factor in the determination of the prognosis is the presence or absence of metastasis. In this series of 20 cases there was enlargement of the regional nodes in 10 at the initial examination in the Chemosurgery Clinic. In the group of patients with enlarged regional nodes successful results were attained in 2 (20 per cent), while in the group without enlargement successful results were obtained in 5 (50 per cent).

In the group of cases in which there was initial enlargement of the lymph nodes surgical dissection was carried out in 6 cases and in all but 1 of those melanoma was demonstrated. In the other 4 cases there were obvious metastatic masses but dissections were not recommended because of extensive involvement or poor general condition. In 1 case a successful result was obtained despite preauricular and cervical metastases; the preauricular mass was chemosurgically excised and the cervical nodes were surgically dissected by Dr. E. R. Schmidt. A successful result was also obtained in a patient in whom the dissected regional nodes showed only lymphadenitis (fig. 2).

In the group which showed no initial enlargement of the regional nodes, metastases subsequently developed in 4 patients. In only 1 of these were the metastases situated in regional nodes where dissection was feasible, and in this case a successful result was attained (fig. 1).

PREVENTION OF MELANOMA BY THE REMOVAL OF NEVI

Since about three out of four melanomas arise in nevi, it is possible to prevent many of them by the removal of nevi which, due to their type, location or behavior, are thought to have malignant potentialities.

The most dangerous type of nevus is the flat or slightly elevated brown or black macule in which the neval cells involve the epidermodermal junction—the so-called junctional nevus (fig. 6). This type of nevus is the commonest one found on the plantar and palmar surfaces but it is not uncommon elsewhere on the extremities and on the scrotum. It may arise at any other point on the body surface, but it occurs much less frequently than the common mole or intradermal nevus. The intradermal nevus rarely undergoes melanomatous change, but it seems advisable to remove those that are in regions subjected to repeated trauma, such as the belt line, the shoulder strap area, the whisker area and the feet. The presence of junctional involvement in 12 per cent of the intradermal nevi in adults, as demonstrated by Allen,[5] is further reason for the removal of common moles from areas which are much traumatized. Certainly, any change in size, coloration or consistency, as well as any ulceration, infection or tumor growth, calls for immediate removal of nevi, whether of the junctional, intradermal or compound type.

The microscopic control of excision afforded by the chemosurgical technic is advantageous in the treatment of nevi because the amount of tissue removed can readily be altered as indicated by the microscopic diagnosis. Thus, if the lesion proves to be a junctional or compound

5. Allen, A. C.: Reorientation on the Histogenesis and Clinical Significance of Cutaneous Nevi and Melanomas, Cancer **2**:28 (Jan.) 1949.

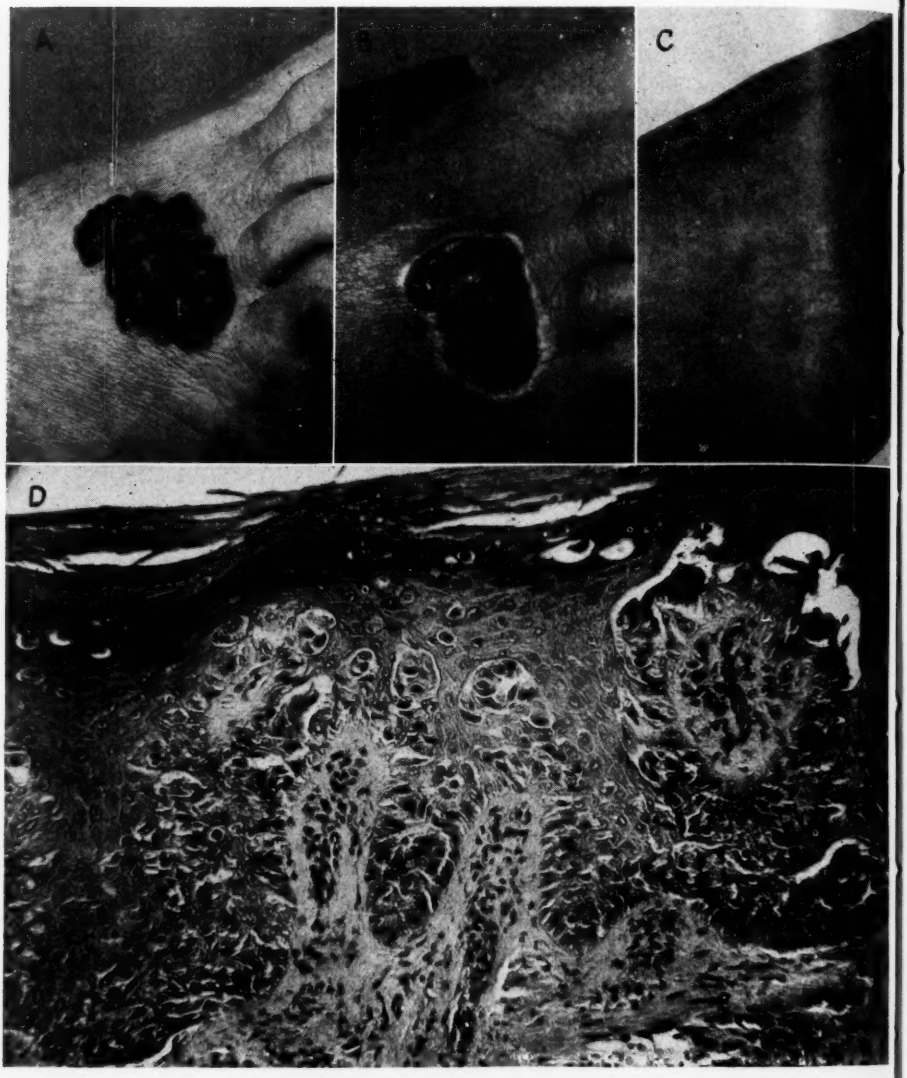

Fig. 6.—*A*, junctional nevus in a patient 50 years of age. The lesion had increased in size sixfold in ten years, and blisters often formed on the surface due to irritation by the shoes. *B*, granulation tissue after chemosurgical removal. *C*, healed lesion five years later. *D*, junctional nevus with considerable proliferative activity.

nevus wider removal may readily be carried out, while if the nevus is an intradermal nevus more conservative removal is justified. Moreover, if any incipient melanomatous or other malignant change is occurring in a nevus it may be detected and more radical measures taken.

A total of 195 nevi were chemosurgically excised during the past fourteen years. Of these, 170 proved to be intradermal, while 7 were junctional and 11 were compound nevi. In this entire group, only 1 case of melanoma developed. In this case a growing, infected, junctional nevus was removed from the foot and, although the primary lesion did not recur, the patient died two and one-half years later of inguinal metastases which could not be controlled by a radical block dissection. There is little doubt that there was melanoma in this junctional nevus

End Results After Five Years in the Treatment of Melanoma

Author	Treatment	No. of Cases	Successful Results	
			No.	Percentage
Mohs	Chemosurgical	20	7	35
Scharnagel (Acta Radiol. **14**: 473, 1933)	Surgical and radiation *	49	19	38.7
Ackerman (Am. J. Clin. Path. **18**: 602, 1948)	Surgical †	21	8	38
Cholnoky (Ann. Surg. **113**: 392, 1941)	Surgical	26	9	34.6
Adair (Surg., Gynec. & Obst. **62**: 406, 1936)	Surgical	125	35	28
DeWeese (J. A. M. A. **138**: 1026, 1948)	Surgical	62	16	25.4
Taussig and Torrey (California & West. Med. **52**: 15, 1940)	Surgical	35	7	20
Daland and Holmes (New England J. Med. **220**: 651, 1939)	Surgical	82	15	18.3
Pack and associates [6]	Surgical	852	?	17.7 and 15.6 ‡
Affleck (Am. J. Cancer **27**: 120, 1936)	Surgical	170	4	2.3

* Compilation of results at Radiumhemmet, Stockholm.
† This group was limited to cases in which radical excision and lymph node dissection were done; in the entire group of 43 treated cases the survival rate was 19 per cent.
‡ Localized melanoma, 17.7 per cent; melanoma with metastatic regional nodes, 15.6 per cent. Pack's series included a number of cases that would be considered inoperable by most surgeons.

prior to excision, but it was inadvertently missed in the examination of the sections. This case emphasizes the importance of a more thorough examination of the specimens when junctional components are found on microscopic examination of a nevus.

COMMENT

In consideration of the advantages and disadvantages of a method for the treatment of melanoma the chief consideration is the degree of reliability. The end result after five years of 35 per cent successful results attained with chemosurgical treatment is about the same as the best results obtained with radical surgery (table). Significant of the effectiveness of chemosurgery is the fact that the primary lesion was

eradicated in 19 of the 20 cases (95 per cent). The single unsuccessfully treated primary lesion was that of a patient who died of coronary occlusion while under chemosurgical treatment for recurrent melanoma in the conjunctiva of a lower eyelid. I have found no series of cases in the literature with such a high rate of cure of the primary melanoma. Pack [6] mentioned local recurrence in 28.4 per cent of his cases, and Farrell [7] reported 30 per cent.

However, there are certain cases in which surgical treatment is preferable. For example, the occurrence of metastases widely seeded along the lympatic vessels of an extremity would necessitate amputation of the limb. Fortunately, in my experience at least, this situation is not common, and I feel that wide chemosurgical removal of the primary melanoma and then block dissection of the regional lymph node–bearing tissues, when indicated, is a sufficiently radical approach for the majority of cases of melanoma.

If the conservative chemosurgical treatment herein outlined is capable of eradicating 95 per cent of the primary melanomas there would seem to be no justification for more radical removal. It is granted, however, that a successful result with this more conservative approach may depend on the most careful and skilful evaluation of the clinical and microscopic features of the individual case.

Melanomas vary widely in their degree of malignancy, and the microscopic study of the tissues carried out during the initial stages of chemosurgical treatment makes possible a more accurate estimate of malignancy. Then, since the procedure is carried out in stages, treatment may be radical or conservative as the individual situation may require.

An incidental advantage of the chemosurgical treatment is that in cases in which the clinical diagnosis is not clear it is safe conservatively to remove the abnormal tissue for microscopic study. If the lesion proves to be a nondangerous one such as pigmented basal cell carcinoma, basal cell carcinoma arising in a nevus, pigmented fibrosing angioma, granuloma pyogenicum, hemangioma or seborrheic keratosis (fig. 4), it is possible to stop the excision at a very conservative level. However, if the suspected lesion proves to be a melanoma, treatment is continued until sufficiently radical removal has been accomplished.

Another advantage beside the reliability and the conservatism of the chemosurgical treatment of melanoma is the low mortality rate. In this series of 20 cases there was only one death during treatment, and

6. Pack, G. T.; Scharnagel, I. M., and Marfet, M.: The Principle of Excision and Dissection in Continuity for Primary and Metastatic Melanoma of the Skin, Surgery **17**:849 (June) 1945.

7. Farrell, H. J.: Cutaneous Melanomas with Special Reference to Prognosis, Arch. Dermat. & Syph. **26**:110 (July) 1932.

this death really was not a result of the treatment; the patient died of coronary occlusion while under treatment for a recurrent melanomatous deposit in the conjunctiva of an eyelid.

The chemosurgical technic often facilitates the removal of melanomas in regions in which radical surgical removal would be difficult and excessively mutilating. For example, a melanoma arising on the nasal septum was widely removed on one side of the septal cartilage so that healing took place without a hole through the septum and without any visible defect. The patient had remained free of recurrence after three years, which period of nonrecurrence is one year longer than that in any previously reported case of melanoma of the nasal mucosa.

Radiation therapy and electrocoagulation are not recommended in the treatment of melanoma. Most melanomas are radioresistant, and therefore radiotherapy should be avoided except for the palliative treatment of inoperable lesions. Rather convincing evidence that electrosurgical procedures which produce tissue steam are likely to force viable melanoma cells into the lymphatics was recorded by Amadon.[8] Therefore, while electrosurgical removal of the main neoplastic mass is often carried out as a time-saving procedure prior to chemosurgical treatment of epithelioma, it is advisable to avoid this practice in the treatment of melanoma. That the action of chemical fixatives has no tendency to increase metastasis has been demonstrated in animal experiments [1a] and confirmed by clinical experience with the chemosurgical method.

SUMMARY AND CONCLUSIONS

The systematic microscopic control of excision which characterizes the chemosurgical method is useful in assuring the complete removal of cutaneous melanomas. However, it is necessary to remove an additional zone of tissue after a melanoma-free level has been reached because of the danger of satellite deposits in the surrounding lymphatics. The width of this extra zone is varied in proportion to the size and the malignancy of the melanoma. The regional nodes are surgically dissected if enlarged or if the size and degree of malignancy of the primary lesion warrant a prophylactic dissection of nonpalpable nodes.

In a consecutive series of 20 cases of melanoma successful results were obtained in 7 (35 per cent). The primary melanomas apparently were eradicated in 19 of the 20 cases (95 per cent). These results compare favorably with the best results reported in the literature by other workers who used considerably more radical procedures.

Only one death occurred during treatment, and this could not be attributed to the effects of the surgical operation.

1300 University Avenue.

8. Amadon, P. D.: Electrocoagulation of the Melanoma and Its Dangers, Surg., Gynec. & Obst. **56**:943 (May) 1933.

PECULIAR DEFORMITY OF HANDS OCCURRING IN EPIDERMOLYSIS BULLOSA

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THE DISEASE known as epidermolysis bullosa was first described by Tilbury Fox in 1879.[1] Since then many case reports have been published, and, although the disease is rare, individual cases are not now worthy of reporting unless they present some unusual feature. Efforts of classification into congenital types and acquired types, hereditary or nonhereditary, have been repeatedly made. Tulipan[2] divided the chief types into three groups: simplex, dystrophica (dominant) and dystrophica (recessive), according to the clinical features. Becker and Obermayer[3] recognized only two forms: epidermolysis bullosa simplex and epidermolysis bullosa dystrophica. Most recorded cases have presented the following common features: The condition appears at birth, or shortly afterward, and bullae appear in response to slight trauma and most frequently on the parts most exposed to trauma—the extremities, especially near joints.

We herein report a rare case showing a peculiar deformity of the hands resulting from the bullae of epidermolysis bullosa. A search of the literature revealed no other such occurrence, although deformities of the nails of hands and feet were recorded by Guy[4] and atrophic changes in the skin of the hands and fingers by Calhoun and Brown,[5] Touraine and Dereu[6] and others. The present patient also showed conjunctival lesions, which are rare in the experience of some observers

1. Fox, T.: Congenital Ulceration of Skin (Two Cases) with Pemphigus Eruption and Arrest of Development Generally, Lancet **1**:766, 1879.

2. Tulipan, L.: Epidermolysis Bullosa Dystrophica (Recessive Type): Report of Case, Arch. Dermat. & Syph. **37**:22 (Jan.) 1938.

3. Becker, W. S., and Obermayer, M. E.: Modern Dermatology and Syphilology, ed. 2, Philadelphia, J. B. Lippincott Company, 1947, p. 73.

4. Guy, W. H.: Epidermolysis Bullosa, Arch. Dermat. & Syph. **15**:30 (Jan.) 1927.

5. Calhoun, T. S., and Brown, W. P.: Epidermolysis Bullosa, Arch. Dermat. & Syph. **11**:185 (Feb.) 1925.

6. Touraine, A., and Dereu, C.: Congenital Bullous Epidermolysis (Dystrophic type), Bull. Soc. franç. de dermat. et syph. **47**:41 (Feb.) 1940.

but not too uncommon according to Tobias.[7] Many authors stated that one of the diagnostic necessities of this disease is a hereditary history, but many cases were recorded by Guy,[4] Smith[8] and others in which this history was not obtained. Smith[8] stated that, whereas the disease is usually hereditary, behaving as a mendelian dominant, isolated cases with no family history are not exceedingly rare and indeed it is likely that each affected family had the origin of the disease in one spontaneous, noninherited case. In the case under discussion here was no history of the disease in parents, grandparents, siblings or cousins.

Fig. 1.—The patient at the age of 5, with beginning malformation of the fingers.

REPORT OF A CASE

G. O., a white man aged 36, was referred to one of us (M. H. C.) by Dr. J. E. Kempter, of Chambersburg, Pa., in February 1949 for relief of an incurable skin disease complicated by a severe deformity of both hands, which was gradually incapacitating him from earning his living as a sign painter. His mother had first noted a blister on one of the fingers when he was 3 days old. A few days later it was noted that rubbing his ankles together would form a "water blister." At the age of 6 months blisters were present "all over" his body. As he developed, the disease progressed, sores appeared, especially over the joints, and the nails of his fingers and toes fell off. Before he entered grade school his fingers grew together and formed fists, leaving only the thumbs free (fig. 1). Later, the thumbs also became encased. The course of the disease was characterized by remissions and exacer-

7. Tobias, N.: Lesions of the Mucus Membranes in Epidermolysis Bullosa, Arch. Dermat. & Syph. **18**:224 (Aug.) 1928.

8. Smith, S. F.: Epidermolysis Bullosa Non-Hereditaria, Non-Congenita, Urol. & Cutan. Rev. **31**:243 (April) 1927.

bations, while the hands became progressively more deformed, appearing much like amputation stumps encased in scar tissue as early as 1936. In 1947 the end of the left scar tissue mitt began to ulcerate.

Physical Examination.—The temperature was 97.8 F.; the pulse rate was 72; respirations were 18 per minute, and the blood pressure was 95 systolic and 55 diastolic. The patient was a thin, underdeveloped white man, in no acute distress, complaining of inability to use his hands and dimness of vision in the left eye. There was no cyanosis, edema, jaundice or unusual pallor of the skin. Most of the emaciated body surface, and especially the hands, feet and all bony prominences,

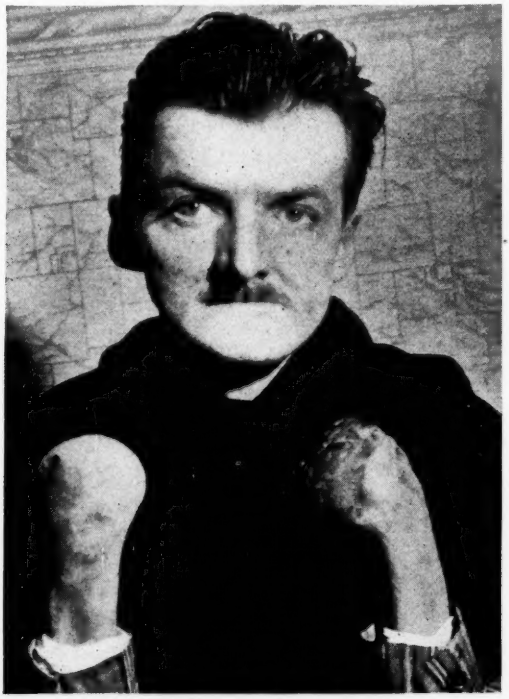

Fig. 2.—The patient at the age of 36, with increased malformation of the hands.

including the elbows, the knees, the scapulas, the lower portion of the spine and the hips, showed the disease, consisting of essentially the same condition everywhere but in various states of development. The minimal abnormality was a simple diffuse dryness and wrinkling of the epidermis, seen best over the abdomen. Vesicles, shallow irregular ulcers and crusts were profuse near the joints and present to a lesser extent elsewhere. The hands were most severely affected; all fingers were contracted maximally and covered by a mitt of smooth scar tissue. The right hand was smoothly encased, as may be seen in figure 2. The distal two thirds of the scar tissue bag which had encased the left hand had ulcerated away, exposing the clutched fingers, which were covered with a foul-smelling, moist, yellowish, half-

necrotic type of granulation tissue (fig. 2). The fingers could be felt when they contracted within the scar tissue mitt on the right side, and a rippling wave could be seen when the patient moved them. The toes had no nails. All teeth had been extracted (dental plates could not be worn because of intermittent bullous lesions on the buccal mucosa). There were lesions of epidermolysis bullosa on the conjunctiva and cornea of each eye, with the lesions on the cornea of the left eye more pronounced.

Fig. 3.—Roentgenogram of the right hand taken in June 1948.

The examination notes of the consulting ophthalmologist were as follows:

The face showed a butterfly-like arrangement of reddened skin with a few points of pus, and in these areas there had been much vesicle formation. The lower eyelids were normal. At the inner third of each upper eyelid on the inner surface

there was reddening of the conjunctiva on the bulbar surface. This had caused a tendency to eversion of the inner third of the upper eyelids. The bulbar conjunctiva looked normal. The corneas were clear. The pupils were normal and reacted to light. Exophthalmometer readings and tension to finger palpation were normal. When the patient looked down, it could be readily seen that the inner third of the upper lid was slightly shortened relative to the remainder of the lid.

Fig. 4.—Roentgenogram of the right hand taken in June 1948.

Refraction: Right eye: Vision was 20/20—4; Jaeger 1 was read at 12 to 18 inches (30 to 46 cm.)

Left eye: Vision was 20/70 and was not improved with the pin hole disk; Jaeger 1 was read at 17 inches (43 cm.).

Ophthalmoscopic Study: Right eye: Corneal opacities were present; the disk was normal; the macula was clear, and the peripheral fundus was normal except for one small spot of pigment in the lower nasal portion of the fundus.

Left eye: Corneal opacities made it difficult to see the fundus clearly. The disk was normal. There was a questionable small lesion of the upper macula; otherwise observations were normal.

Slit Lamp Examination: Right eye: On the lower half of the cornea there were subepithelial opacities. These did not involve the pupillary space. The lens was clear and the aqueous ray negative.

Left eye: There were more opacities which were subepithelial and did not take a stain. They were over the lower half of the cornea and lower part of pupillary area. On the posterior surface there were old lesions of keratitis punctata. The lens exhibited posterior cortical opacities (complicated cataracts). There were two Koeppe nodules seen on the iris margin before dilation.

Fields: The fields were full for form.

Tension: The tension was normal to finger palpation.

Impression: In this case there were exhibited ocular lesions of epidermolysis bullosa on the conjunctivas and corneas of both eyes with the lesions on the cornea of the left eye more pronounced and evidence of intraocular inflammation of the left eye. The lesions were in a resting state at the time of examination. The rest of the physical examination revealed essentially normal conditions.

Laboratory Data.—The serologic test for syphilis gave negative reactions. Roentgenograms of the hands showed fingers to be contracted and dislocated; the carpal bones appeared normal (figs. 3 and 4). A complete blood count was normal, with 27 mg. of nonprotein nitrogen, 85 mg. of sugar, 3.8 mg. of phosphorus and 10.5 mg. of calcium per hundred cubic centimeters. There was excretion of 9.4 mg. of 17-ketosteroids per twenty-four hours, and the serum proteins were 7.8 mg., with 4.38 mg. of albumin and 3.43 mg. of globulin, in 1944. In view of Turner and Obermayer's [9] and Zeligman and Baum's [10] finding of porphyria in cases of epidermolysis bullosa, the urine was examined for porphyrins, with negative results. Several biopsy specimens were examined and found to show lesions similar to those described in other cases of this disease.

COMMENT

Since the cause of epidermolysis bullosa is unknown the treatment has been necessarily empiric. Cannon, Sanders and Rankin [11] reported 4 cases in which bacteriologic studies isolated the group G strain of the hemolytic streptococci from the bullous lesions and in which the condition showed pronounced improvement after sulfanilamide had been administered. In the course of years our patient received many months of treatment with sulfonamides and penicillin with no relief. Various writers have reported treatment with large doses of vitamins, calcium, thyroid, pituitary preparations and roentgen rays, with no suc-

9. Turner, W. J., and Obermayer, M. E.: Studies on Porphyria: II. A Case of Porphyria Accompanied with Epidermolysis Bullosa, Hypertrichosis and Melanosis, Arch. Dermat. & Syph. **37**:549 (April) 1938.

10. Zeligman, I., and Baum, M.: Porphyric Bullous Dermatitis, Arch. Dermat. & Syph. **58**:4 (Oct.) 1948.

11. Cannon, B. A.; Sanders, M., and Rankin, J. L.: Epidermolysis Bullosa: A Clinical and Bacteriologic Study; Report of Four Cases, Arch. Dermat. & Syph. **42**:884 (Nov.) 1940.

cess. This patient received his fair share of these treatment measures at the hands of his many attending physicians, for he sought relief from many sources. We are inclined to agree with the belief expressed by Waddill [12] that prevention of secondary infection of the lesions is probably all the treatment that is justified at the present time. Efforts have been made to interest a plastic surgeon in liberating the fingers or a thumb from the sac of scar tissue so that the patient may have better use of what remains of his hands, but an understandable reluctance has been shown for any attempt at restorative surgical procedures, in the face of almost certain failure of healing.

SUMMARY

A case of epidermolysis bullosa is reported in which there was a peculiar and striking deformity of the hands following the repeated rupture and healing of bullous lesions over many years. Rare ocular lesions also were presented.

12. Waddill, G. M., Jr.: Epidermolysis Bullosa Hereditaria, J. Pediat. **16**:500 (April) 1940.

TREATMENT OF ONYCHOMYCOSIS WITH AMMONIACAL SILVER NITRATE SOLUTION

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AND
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AMMONIACAL silver nitrate solution is a solution of a complex silver salt that has been recently used in the treatment of onychomycosis. Nickerson and White [1] reported excellent success in the topical use of ammoniacal silver nitrate solution (Condit Co.) in chronic fungous infections of the nails.

Because of the lack of effective measures for onychomycosis, especially when the condition is due to Trichophyton rubrum (i. e., Trichophyton purpureum), this new approach using the complex silver salt was deemed worthy of trial. The purpose of this short paper is to report on 25 cases of onychomycosis treated with ammoniacal silver nitrate solution.

TYPES OF CASES STUDIED

Twenty-five cases of fungous infections of the finger nails and toe nails were studied. Of the total, 18 were shown to be caused by T. rubrum and 7 were due to Candida albicans (i. e., Monilia albicans). Generally, nails infected with T. rubrum are opaque, lusterless, friable and yellowish. Varying degrees of dystrophy may also be present. This dystrophy is manifested by unevenness of the nail plate, separation of the nail and subungual hyperkeratosis. The onset is slow and insidious. Frequently many nails are involved. Little or no paronychial reaction is present. White or yellow streaking due to the separation of the nail plate from the bed may appear. In those cases due to C. albicans the nail plate may be hard, thickened and deformed, while the luster may remain unchanged. Paronychia is generally present. The diagnosis was made by clinical appearance, microscopically by the direct slide method

From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School, Dr. Marion B. Sulzberger, chairman, and the Skin and Cancer Unit of University Hospital.

1. Nickerson, W. J., and White, S. J.: Therapeutic Value of Ammoniacal Silver Nitrate in Fungous Infections of the Nails, Arch. Dermat. & Syph. **57**:935 (June) 1948.

and by culture on Sabouraud's or corn meal mediums. Patients ranged in age from 23 to 64 years. The onychomycosis had been present for variable periods ranging from three months to about fifteen years, but only 1 patient had had the disease for less than one year. Two patients had had a fungous infection of the nails for a period of fifteen years.

METHOD

Ammoniacal silver nitrate solution, a liquid of high purity, was supplied by P. L. Condit Co. The silver content of the solution was between 29.50 and 30.50 per cent, and the ammonia content, 9.35 to 9.60 per cent. The ratio of silver to ammonia was 3.10 to 1.00. The solution was applied in the clinic at weekly intervals, and the entire procedure was carried out exactly as suggested by Nickerson and White.[1] Prior to each treatment the patient was instructed to clip and scrape the nails. The solution was applied by capillary pipet to all the involved nails. A few patients complained of a slight burning or stinging sensation, and some temporary erythema and swelling were noted after the first few applications. But, just as was reported by Nickerson and White,[1] in our series also no serious contraindication to the further use of the solution was encountered. The average number of treatments administered was ten. The least number was six, and the most given to 1 patient was fifteen.

RESULTS

The response to treatment with ammoniacal silver nitrate solution in the 18 cases of T. rubrum infections of the nails was not satisfactory. There seemed to be temporary clinical improvement in 6 cases.

In the 7 cases caused by C. albicans, decided clinical improvement was noted in 5; in only 2 cases was there no improvement. In no case was there a positive direct smear after the treatment.

COMMENT

In a series of 25 cases of fungous infections of the nails caused by either T. rubrum or C. albicans, we found that the repeated application of ammoniacal silver nitrate solution brought about little or no clinical or laboratory evidences of improvement in those caused by the T. rubrum. This unfavorable result was not unexpected when one considers the site of the infecting microorganisms shown in the histologic examinations of infected nails performed by Sagher.[2] He demonstrated that in T. rubrum infection the fungi were observed only in the deepest and middle layer of the nail plate. He also showed that the fungi were located in the medial portion and at the nail root.

In those cases caused by C. albicans, decided clinical and mycologic improvement were noted in the cases in which there was ammoniacal silver nitrate therapy. This, too, was not unexpected, because of the superficial nature of the invasion by this type of yeastlike cell.

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2. Sagher, F.: Histologic Examinations of Fungous Infections of the Nails, J. Invest. Dermat. **2**:337 (Nov.) 1948.

CONCLUSIONS

In 18 cases of chronic resistant fungous infections of the nails caused by T. rubrum, we were unable to confirm the good results obtained by Nickerson and White [1] with applications of a solution of ammoniacal silver nitrate.

Our results in those infections of the nails caused by C. albicans were good and fully confirmed those of Nickerson and White.[1]

This method of treatment may be considered a valuable addition for the treatment of onychomycosis due to C. albicans.

THERAPEUTIC VALUE OF CHLORAMPHENICOL IN A GROUP OF DERMATOSES OF ESTABLISHED OR QUESTIONABLE VIRUS ETIOLOGY

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THE AVAILABILITY of chloramphenicol (chloromycetin® [1]), an agent found effective against certain viruses, suggested its use as a therapeutic agent in the group of dermatoses selected for this study.

I have treated 76 patients with the agent up to the time of this report, and the results have been sufficiently interesting that I believe a preliminary report is justified. A group of dermatoses in which there has been an established or questionable virus etiology were included in this study. The erratic response of several of these diseases to all forms of therapy is well known, and they therefore offered an excellent therapeutic test for the use of chloramphenicol.

Thirteen cases representing the erythema multiforme group, 7 cases of pemphigus vulgaris, 8 cases of herpes zoster, 5 cases of herpes simplex, 32 cases representing the verruca group, 3 cases of molluscum contagiosum, 3 cases of varicella and 5 cases of dermatitis herpetiformis were studied. The age ranged from 3 to 53 years; 41 patients were male and 28 were female; of the 7 children in the group, 3 were boys, and 4, girls. The duration of the dermatoses varied from two days to eighteen months.

Chloramphenicol was supplied in 250 mg. capsules for oral administration. The total daily dose ranged from 500 to 2,000 mg., and the drug was administered in half-size doses to children. No serious side effects were noted. The reactions encountered were minor, consisting of headache and nausea, and appeared only when the daily dose exceeded 1,000 mg. Reduction of the dose or withdrawal of the drug for twenty-four hours controlled these reactions, and no allergic manifestations or sensitivity to the drug was encountered in this series.

Topical applications to control infection and pruritus were used where indicated. The treatment was continued over a period judged sufficient to establish clinical improvement, which varied from two to six weeks. During the course of treatment no contraindication to the drug was encountered.

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1. Dr. E. A. Sharp, Parke, Davis & Company, Detroit, supplied the chloramphenicol (chloromycetin®) used in this study.

COMMENT

The analysis of the therapeutic response to chloramphenicol administered orally revealed no specific advantage of the treatment over other recognized therapeutic procedures used for this group of diseases. Of the 76 patients treated, 4 (5.2 per cent) were classified as cured, and 20 (26.3 per cent) manifested definite clinical improvement; in the remaining 52 patients (68.5 per cent) treatment was considered a failure. Minor untoward reactions, headache and nausea occurred in 4 patients (5.2 per cent). Clinical cures were obtained in 2 cases each of erythema multiforme and herpes zoster, in which the clinical response was dramatic. Uniform failure was recorded in pemphigus vulgaris, varicella and the majority of cases of dermatitis herpetiformis and diseases in

Results of Treatment of Dermatoses of Established or Questionable Virus Etiology with Chloramphenicol

Disease	No. of Cases	Duration	Daily Dose	Period of Treatment	No. Cured	No. Improved	No. of Failures
Erythema multiforme bullosum.	6	2 wk.-3 mo.	1,000-1,500 mg.	2-3 wk.	2	2	2
Erythema multiforme papulosum	6	2-4 wk.	750 mg.	3 wk.	0	3	3
Stevens-Johnson syndrome.....	1	3 wk.	1,500 mg.	4 wk.	0	0	1
Pemphigus vulgaris.....	7	4-9 mo.	1,500-2,000 mg.	3-6 wk.	0	0	7
Herpes zoster.....	8	3-14 days	750 mg.	7-14 days	2	4	2
Herpes simplex.....	5	2-5 days	750 mg.	7-14 days	0	3	2
Verruca plantaris.....	4	6-14 mo.	750 mg.	3 wk.	0	0	4
Verruca vulgaris.....	24	3-18 mo.	750 mg.	4-6 wk.	0	4	20
Condylomata acuminata.....	4	6 wk.-3 mo.	750 mg.	2-3 wk.	0	0	4
Molluscum contagiosum.....	3	3 wk.-2 mo.	500 mg.	1-3 wk.	0	2	1
Dermatitis herpetiformis.....	5	4-8 mo.	1,500 mg.	3-6 wk.	0	2	3
Varicella	3	4 wk.	500 mg.	2-3 wk.	0	0	3

the verruca group. The treatment of verruca with chloramphenicol paralleled a previous experience with the use of aureomycin.[2] It is interesting to report that the patients with varicella belonged to the same family. Immediately after the appearance of the eruption in the first member of the family, prophylactic medication with chloramphenicol was given to the other 2 children for a period of ten days without any clinical inhibitory effect. Medication was continued in all patients for a period of two weeks without altering the clinical symptoms or course of the disease.

Definite clinical improvement was manifested in 20 patients, including those with erythema multiforme bullosum (2 cases), herpes zoster (4 cases), herpes simplex (3 cases), verruca vulgaris (4 cases), molluscum contagiosum (2 cases) and dermatitis herpetiformis (2 cases). This response was promising and warrants further study. Despite the

2. Beinhauer, L. G., and Gibson, W. S.: Aureomycin in the Treatment of Verruca Vulgaris: Urol. & Cutan. Rev. **53**:547-548 (Sept.) 1949.

recorded failures (68.5 per cent) in this series, a further trial with chloramphenicol is indicated, as any approach in the treatment of a group of resistant dermatoses which can effect a cure in even a small percentage should not be discarded.

SUMMARY

Seventy-six cases of dermatoses of recognized and questionable virus etiology were treated with chloramphenicol.

Clinical response was not striking, and the percentage of cures was low.

Untoward reactions were minor, and the drug was well tolerated.

Further clinical study is warranted to determine the efficacy of this drug.

5026 Jenkins Arcade (22).

BLOOD VESSELS OF THE SKIN IN CHRONIC VENOUS INSUFFICIENCY

Clinical and Pathologic Study

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THE CLINICAL phenomena associated with venous stasis in the lower extremities and the sequelae thereof are among the commonest of entities seen in the practice of medicine. It has been estimated [1] that 10 to 17 per cent of the population are afflicted with varicose veins and their complications.

That there is an important relation between chronic venous insufficiency and the subsequent (or concomitant) development of cutaneous changes in adjacent or overlying areas of skin or both has not been questioned, but the mode of development of such changes has long been a matter of much conjecture.

The purpose of this investigation was to determine what, if any, pathologic changes occurred in the blood vessels of the skin of the lower extremities in patients who showed clinical manifestations of chronic insufficiency of the venous return of blood from these areas.

CHRONIC VENOUS INSUFFICIENCY

Definition.—Chronic venous insufficiency has been defined [2] as a pathologic condition of the tissues of the lower extremity which is the result of insufficiency or stasis of the venous blood flow. It may be localized, or it may involve the entire extremity.

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* From the Division of Medicine, Mayo Clinic.

This paper is an abridgment of a thesis submitted by Dr. Kulwin to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Dermatology and Syphilology.

1. Larson, R. A., and Smith, F. L.: Varicose Veins: Evaluation of Observations in 491 Cases, Proc. Staff Meet., Mayo Clin. **18**: 400-403 (Oct. 20) 1943.

2. Allen, E. V.; Barker, N. W., and Hines, E. A., Jr.: Peripheral Vascular Diseases, Philadelphia, W. B. Saunders Company, 1946, p. 666.

Causes.—The causes of chronic venous insufficiency are multiple and have been outlined by Allen, Barker and Hines [2] as follows: (1) obstruction to one of the main veins of the extremity, particularly the iliofemoral, as a result of thrombophlebitis, neoplastic invasion or external venous pressure, (2) incompetency of valves of the iliofemoral vein resulting from iliofemoral thrombophlebitis without permanent obstruction of the iliofemoral vein and (3) varicose veins of the primary type, particularly those of long standing or considerable extent.

Factors causing external venous pressure which may lead, eventually, to a state of chronic venous insufficiency include pregnancy [3] and persistently increased intra-abdominal pressure due to abdominal tumors.[4]

Varicose veins of the primary type are those which develop spontaneously. Their development is abetted by such factors as overweight, enforced inactivity,[5] the upright posture of man [6] and endocrine dysfunction. Miller and Sparrow [7] expressed the belief that certain undetermined hereditary factors play a role in the predisposition of certain persons to the development of varicose veins.

It should be kept in mind that the varicosed vessels do not always show on the surface. They may be concealed by the skin and its fatty layer and, very often, by the secondary changes (edema, pigmentation and dystrophy) which they themselves have produced. Conversely, varicosities of the main trunks may exist without cutaneous changes, even though the varices have developed to such an extent that normal venous circulation in the limb does not exist. Delater [8] expressed the opinion that in such a case blood from the superficial cutaneous vessels follows a direction other than that in the varicosed veins—probably via the communicating veins to a deep plexus which is sufficient for the task.

Clinical Manifestations.—The loss of circulatory equilibrium attendant on chronic venous insufficiency inaugurates a train of path-

3. Veal, J. R., and Hussey, H. H.: The Venous Circulation in the Lower Extremities During Pregnancy, Surg., Gynec. & Obst. **72:** 841-847 (May) 1941.

4. Adams, J. C.: Etiological Factors in Varicose Veins of the Lower Extremities, Surg., Gynec. & Obst. **69:** 717-725 (Dec.) 1939.

5. Barber, R. F.: Treatment of Varicose Veins and Ulcers, Am. J. Surg. **36:** 386-388 (April) 1937.

6. de Takáts, G.: Varicose Veins, in Christopher, F.: A Textbook of Surgery, Philadelphia, W. B. Saunders Company, 1936, pp. 168-175.

7. Miller, R. P., and Sparrow, T. D.: The Pathogenesis, Diagnosis, and Treatment of Varicose Veins and Varicose Ulcers: Analysis of 200 Cases Treated by Upper Saphenous Ligation, North Carolina M. J. **9:**574-579 (Nov.) 1948.

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ologic events,[9] which may include edema, noninflammatory changes in cutaneous structure (for example, loss of hair), inflammatory changes in the skin, changes in the subcutaneous tissue, muscles, bones and joints, venous thrombosis or rupture, ulceration and changes secondary to ulceration (for example, malignant degeneration).

Obvious edema may be the first manifestation of chronic venous insufficiency,[10] inasmuch as it will occur when the amount of collected tissue fluid increases the volume of the limb by as little as 8 per cent.[11]

Varicose eczema, or stasis dermatitis, is usually an intermediary stage between the first appearance of orthostatic edema in the legs and the eventual development of varicose ulcers. It may assume the picture of neurodermatitis (lichen simplex chronicus).[12] The pathogenesis of these cutaneous changes is usually explained on the basis of chronic passive congestion of the skin and subcutaneous tissue, which results from venous stasis in the varicose superficial vessels. Zimmerman[13] expressed the opinion, however, that many of the clinical features of these cases suggest another interpretation, namely, that the cutaneous complications are of inflammatory origin, arising by direct extension from a preexistent phlebitis of the varicose vein. Infra-red photography of the legs, as reported by Zimmerman and Rattner,[14] supports this contention because, if the development of the cutaneous complications herein referred to were dependent on the chronic passive congestion of the skin and subcutaneous tissues, these changes would occur in the portion of the capillary bed which drains into the varicosed vein. But, contrarily, it was demonstrated by Zimmerman and Rattner that immediately beneath an area of dermatitis lies a dilated venous trunk.

Speaking against the foregoing thesis is the rapidity with which these cutaneous lesions will clear up on elevation of the involved extremity without other local or systemic treatment.

Ulceration is the single commonest serious complication of chronic venous insufficiency. It is chiefly a matter of concern because of the disability it produces. The most generally accepted concept of pathogenesis of the ulcers is that they are the result of changes produced

9. Wright, A. D.: Varicose Ulcer, Brit. M. J. **2:** 561-565 (Sept. 26) 1931.

10. Allen, Barker and Hines,[2] p. 667.

11. Drury, A. N., and Jones, N. W.: Observations upon the Rate at Which Oedema Forms When the Veins of the Human Limb Are Congested, Heart **14:**55-70 (April) 1927.

12. Heyerdale, W. W., and Cannon, E. E.: Neurodermatitis Associated with Incompetent Greater Saphenous Veins: Report of a Case, Arch. Dermat. & Syph. **44:** 52-54 (July) 1941.

13. Zimmerman, L. M.: Pathogenesis of the Cutaneous Complications of Varicose Veins, Arch. Dermat. & Syph. **34:** 97-102 (July) 1936.

14. Zimmerman, L. M., and Rattner, H.: Infra-Red Photography of Subcutaneous Veins, Am. J. Surg. **27:** 502 (March) 1935.

in the skin and subcutaneous tissues, which are dependent on stagnation of blood in the dilated and incompetent veins.[15]

Associated Circulatory Changes.—Numerous investigations have been made on the nature of the unphysiologic condition which exists in the presence of chronic venous insufficiency. The abnormal conditions which prevail are based, essentially, on the relative reverse flow of venous blood in the limb.

Normally, the venous blood flows upward in the superficial and deep veins and inward in the communicating veins. With dilatation of the superficial channels and loss of valve action in the superficial

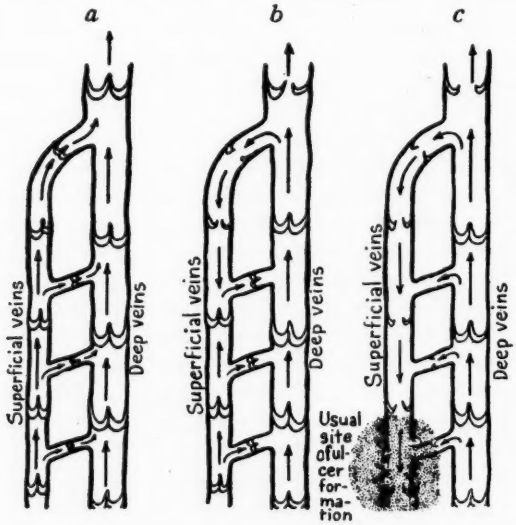

Fig. 1.—(*a*) Normal flow in superficial and deep veins. (*b*) Beginning reflux flow in the superficial veins. (*c*) Complete loss of valve function in the superficial and communicating veins. (Reproduced with permission from McPheeters and Anderson.[15b])

and communicating veins, however, the blood follows the course of gravity and flows downward in the saphenous vessels and outward in the communicating ones (fig. 1).

15. (*a*) Ochsner, A.: Chronic Cutaneous Ulceration of the Lower Extremities, New Orleans M. & S. J. **84:** 594-607 (Feb.) 1932. (*b*) McPheeters, H. O., and Anderson, J. K.: Injection Treatment of Varicose Veins and Hemorrhoids, ed. 2, Philadelphia, F. A. Davis Company, 1939, p. 65. (*c*) Homans, J.: Varicose Veins and Ulcer: Methods of Diagnosis and Treatment, Boston M. & S. J. **187:** 258-266 (Aug. 17) 1922.

Histopathologic Changes in the Skin.—A histologic diagnosis of "stasis dermatitis" or "varicose eczema" cannot be made on the basis of microscopic study alone because the pathologic changes found may be those of a nonspecific dermatitis. The microscopic picture must be correlated with the clinical observations and judged accordingly. The diagnosis of stasis dermatitis is justified only when there are clinical indications of venous stasis; for example, edema, discoloration, varicose veins, other manifestations of venous insufficiency or some combination of them.

The histopathologic anatomy of the skin in varicose eczema was described in detail by Gans.[16]

A study of a single tissue specimen from a varicose ulcer, reported by Golden,[17] did not reveal the presence of any vascular lesions.

Other than the foregoing two reports (Gans,[16] Golden[17]), no description of the cutaneous vascular changes associated with chronic venous insufficiency was found in a search of the literature. It is assumed, therefore, that the present investigation represents the first detailed description of the changes in the arterioles and venules of the skin in this condition.

REPORT OF STUDY

The basic problem which was studied in this investigation may be stated as follows: In patients who show clinical evidence of chronic venous insufficiency, do the blood vessels of the skin in areas of venous insufficiency differ from those in comparable areas of skin in normal persons, and, if so, what is the qualitative nature of the changes?

The general plan of approach to this problem was as follows: Specimens of skin from the lower part of the leg were obtained from a group of patients in whom a diagnosis of chronic venous insufficiency had been made. Specimens of skin from comparable areas in apparently normal persons (that is, normal from the standpoint of there being no evidence of any peripheral vascular disease) were then obtained for comparison.

The group of patients with chronic venous insufficiency was carefully screened to exclude all persons who did not present very definite clinical evidence of such insufficiency, such as varicose veins, edema following thrombophlebitis or brawny induration. The mere presence of dermatitis or an ulcer on the lower portion of the leg without other manifestations was not considered sufficient proof of venous stasis. Control material was obtained in cases in which necropsy was performed

16. Gans, O.: Histologie der Hautkrankheiten, Berlin, Julius Springer, 1927, vol. 2, pp. 158-169.

17. Golden, A.: A Comparison of the Pathologic Anatomy of the Central American Tropical Ulcers and Those of a Variety of Leg Ulcers of North America, South. M. J. **40**: 214-219 (March) 1947.

and in which there was no history of peripheral vascular disease or arterial hypertension. These specimens were obtained from sites comparable to those from which specimens were taken in the cases of chronic venous insufficiency and from persons in approximately the same age range.

The influence of aging on the blood vessels must be taken into account in a study such as this, but, inasmuch as the aging factor was equal in the patients with chronic venous insufficiency and in the control group, it was a common denominator and, as such, could be discounted in the present study.

TABLE 1.—*Age and Sex of Patients in Control Group*

Age, Years	Male	Female	Total
15-24	1	0	1
25-34	0	1	1
35-44	4	0	4
45-54	0	1	1
55-64	5	1	6
65-74	0	1	1
75-84	0	0	0
85-94	0	2	2
Total	10	6	16

TABLE 2.—*Age and Sex of Patients with Chronic Venous Insufficiency*

Age, Years	Male	Female	Total
20-29	3	0	3
30-39	2	3	5
40-49	2	5	7
50-59	3	6	9
60-69	2	1	3
70-79	2	1	3
Total	14	16	30

CLINICAL SURVEY OF MATERIAL

Sixteen control specimens of skin were obtained. The age and sex of patients from whom the material was obtained are given in table 1. Ten of the patients were male, and 6 were female. The oldest was 85, and the youngest, 16 years of age.

Thirty-one specimens of skin were obtained from 30 patients for whom a clinical diagnosis of chronic venous insufficiency had been made. Table 2 gives the distribution of these patients by age and sex. Of these 30 patients, 14 were male and 16 female. The oldest was 76, and the youngest, 24 years of age. The age and sex distribution of these patients approximated that of those in the control group. In this group of 30 patients, the cause of the chronic venous insufficiency was

varicose veins in 25, of whom 19 had primary varicosities (3 unilateral and 16 bilateral) and 6 had superficial varicosities secondary to iliofemoral thrombophlebitis (2 unilateral and 4 bilateral). The distribution of these patients according to duration of disease is shown in table 3. Table 4 lists the causes of the iliofemoral thrombophlebitis in the cases in which there were secondary varicose veins.

The remaining 5 patients had no clinical evidence of varicosities. One had a history of postpneumonic iliofemoral thrombophlebitis without development of varicosities; 1 had a history of fracture of a hip

TABLE 3.—*Clinical Data on Patients with Varicose Veins*

Clinical Type	Duration of Varicosities, Years						
	0-4	5-9	10-14	15-19	20-24	25-29	Total
Varicose veins	6	6	7	4	0	2	25
Primary	2	5	6	4	0	2	19
Unilateral	1	1	0	0	0	1	3
Bilateral	1	4	6	4	0	1	16
Secondary	4	1	1	0	0	0	6
Unilateral	1	0	1	0	0	0	2
Bilateral	3	1	0	0	0	0	4

TABLE 4.—*Etiologic Factors in Patients with Secondary Varicose Veins*

Iliofemoral Thrombophlebitis Associated with:	
Typhoid	1
Pneumonia	1
Pelvic injury	1
Postoperative Iliofemoral Thrombophlebitis	2
Postpartum Iliofemoral Thrombophlebitis	1
Total	6

followed by iliofemoral thrombophlebitis without varicosities, and 3 had a history of induration and edema of the lower extremities for a period of years without definite preceding history of thrombophlebitis or injury.

Eight of the patients showed no evidence of cutaneous complications of the venous stasis. The skin on their legs appeared normal. Thirteen of the patients had stasis dermatitis, and the remaining 9 had ulcerated lesions.

HISTOPATHOLOGIC OBSERVATIONS

In this investigation, attention was concentrated on the vessels at the dermosubdermal junction, first, to establish a degree of uniformity in the size of the vessels studied and, second, because blood vessels smaller than those found at this level could not always be definitely identified as arterioles or venules.

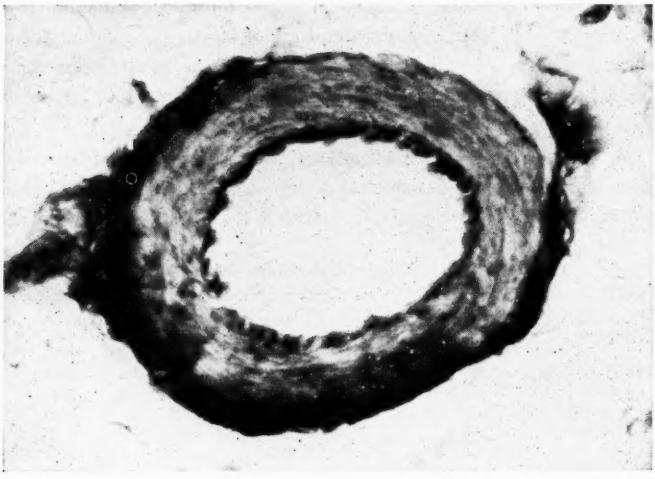

Fig. 2.—A normal cutaneous arteriole from the leg of a boy aged 16 years (elastic tissue–Van Gieson stain, × 415).

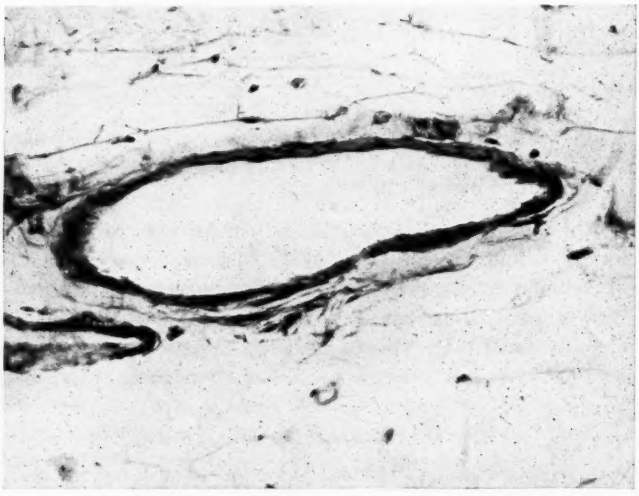

Fig. 3.—A normal cutaneous venule from the leg of a man aged 64 years (elastic tissue–Van Gieson stain, × 250).

Pathologic Changes.—Of the 16 specimens in the control group, abnormal vessels were found in only 1, which was taken from the leg of a man aged 63 years who had died with carcinoma of a kidney and metastatic growths. In the other 15 control specimens, the appearance of the arterioles and venules conformed to the descriptions in standard textbooks of histology. Representative normal vessels are illustrated in figures 2 and 3.

In the group with chronic venous insufficiency, arteriolar structure was studied in 30 specimens. Of these, 5 showed no pathologic change and 25 showed variation from the normal. Of the 5 specimens which showed no evidence of arteriolar damage, 4 were from areas of dermatitis and 1 was from normal skin. In this group of patients with normal arterioles the duration of the chronic venous insufficiency varied from two to ten years. Three of these patients had no evidence of cardiovascular disease; 1 had mild arterial hypertension (150 mm. of mercury systolic and 90 diastolic), and in 1 patient no determination of blood

TABLE 5.—*Clinical Data on Patients with Skin Containing Normal Arterioles*

Type of Venous Insufficiency	Duration, Years	Condition of Skin	Blood Pressure, Mm. of Mercury
Varicose veins	10	Dermatitis	110/70
Varicose veins	2	Dermatitis	104/70
Induration with edema	5	Dermatitis	No record
Varicose veins	6	Dermatitis	128/75
Varicose veins	10	Normal	150/90

pressure was made. The clinical information on these patients is summarized in table 5.

In the remaining 25 specimens—those that showed arteriolar damage—intimal proliferation was seen in 16, in 2 of which elasticization of the intima was also seen, and no intimal change was seen in 9. The internal elastic membrane appeared normal in 22 specimens of 29 in which this structure was examined and showed evidence of fragmentation or reduplication or both in 7. Endothelial hyperplasia was seen in 4 specimens, and thickening of the medial coat of the arterioles was present in 21. Complete obliteration of the arterioles was seen in 3 specimens, all of which were from ulcerated areas. There were no definite changes in the arterioles of the patients with arterial hypertension which might set these persons aside as a distinct group.

Of 30 specimens in which the structure of the venules was studied 15 were normal and 15 showed venular changes. Only 1 specimen showed intimal, endothelial and medial changes. Six specimens showed intimal proliferation; 3 showed endothelial hyperplasia, and 13 showed broadening of the medial layer. Figure 4 shows representative arteriolar changes, and figure 5, typical changes in a venule.

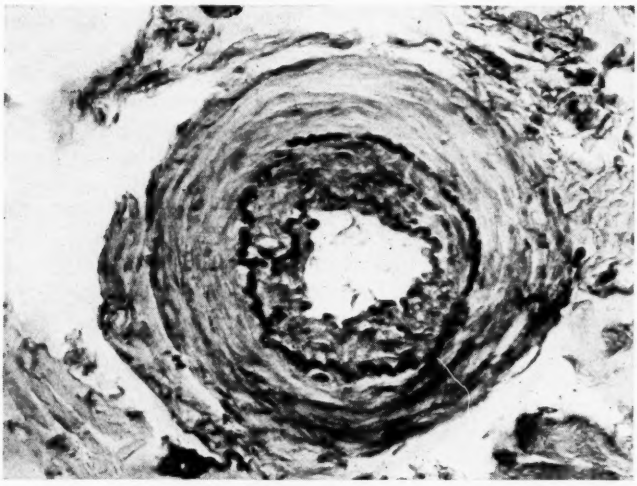

Fig. 4.—A cutaneous arteriole from the skin on the lower part of the leg of a man aged 25 years who eight years previously had had postoperative bilateral iliofemoral thrombophlebitis with subsequent development of bilateral varicosities. His blood pressure was 130 mm. of mercury systolic and 90 diastolic. Note the pronounced intimal proliferation with elasticization thereof and pronounced medial hypertrophy (elastin H stain, × 430).

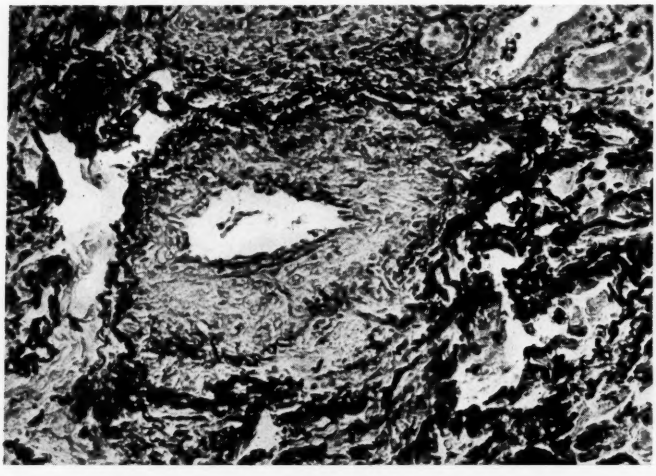

Fig. 5.—A venule from the skin of the leg of a man aged 70 years, who had had bilateral iliofemoral thrombophlebitis thirty-five years previously. He had bilateral varicosities of two years' duration. His blood pressure was 130 mm. of mercury systolic and 85 diastolic. Intimal thickening, endothelial hyperplasia and medial hypertrophy can be seen in this section (elastin H stain, × 200).

A more detailed analysis of the vascular pathologic changes found in this study is reported elsewhere.[18]

COMMENT

No correlation could be made between the duration of the chronic venous insufficiency and the extent of the pathologic changes in the vessels, nor was there any evident relation between the type of vascular pathologic change seen and the origin of the venous insufficiency or any other clinical factors.

Of the 25 specimens that showed arteriolar changes, 8 were from areas of normal skin. This observation would bear testimony to the hypothesis that the arteriolar changes are not necessarily secondary to inflammatory changes in the skin and subcutaneous tissue. Adding proof to this idea is the fact that of the 8 patients in this series with chronic venous insufficiency and normal-appearing skin only 1 showed no evidence of vascular pathologic change.

That arterial ischemia exists in patients of the type herein described, leading to a dermoepidermic necrosis, was postulated by Leriche[19] and was used as the rationale for treating those patients by means of lumbar sympathectomy. De Takáts and associates[20] stated that in their experience approximately 50 per cent of the patients with varicose veins showed evidence of diminished arterial supply as determined by the response of the skin to histamine. According to Allen, Barker and Hines,[21] however, the histamine flare test has little clinical value in the appraisal of peripheral vascular disease.

Mention should be made of the peculiar clinical paradoxes frequently encountered—a severe degree of venous insufficiency without dermatitis or other cutaneous changes in some cases and, conversely, in others a mild degree of incompetence of the venous return of a lower extremity associated with very pronounced cutaneous changes. Both varieties were encountered in this study, but no vascular peculiarities were noted in the skin which might account for them.

SUMMARY AND CONCLUSIONS

The anatomicopathologic features of the blood vessels of the skin in 31 biopsy specimens from 30 cases of chronic venous insufficiency of the lower extremities were studied, together with the clinical features of these cases.

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18. Kulwin, M. H., and Hines, E. A.: Blood Vessels of the Skin in Chronic Venous Insufficiency, Circulation, to be published.

19. Leriche, R.: Surgery of the Sympathetic System: Indications and Results, Ann. Surg. **88**:449-469 (Sept.) 1928.

20. de Takáts, G.; Quint, H.; Tillotson, B. I., and Crittenden, P. J.: The Impairment of Circulation in the Varicose Extremity, Arch. Surg. **18**: 671-686 (Feb.) 1929.

21. Allen, Barker and Hines,[2] p. 122.

Twenty-five specimens, 8 of which were of normal-appearing skin, showed evidence of arteriolar damage in the form of intimal proliferation, fragmentation or reduplication, or both, of the internal elastic membrane, endothelial hyperplasia, medial hypertrophy or some combination thereof.

Fifteen specimens showed evidence of venular pathologic changes in the form of intimal proliferation, endothelial proliferation and hyperplasia, medial hypertrophy or some combination thereof. Five of these specimens were of normal-appearing skin.

As a result of this study, it appears that pathologic changes in the arterioles of the skin are a usual concomitant finding in areas of chronic venous insufficiency of the lower extremities. Changes in the venules exist in about one half of the cases. The causal relation of these changes to cutaneous manifestation of chronic venous insufficiency has not been determined.

Drs. Hamilton Montgomery, Jesse E. Edwards and T. T. Myers of the Mayo Clinic rendered assistance in the course of this investigation.

ATYPICAL KERATOSIS PILARIS

FRANCIS P. COOMBS, M.D.
BROOKLYN
AND
THOMAS BUTTERWORTH, M.D.
READING, PA.

DURING the past fifteen years we have observed at the Pennhurst State School for feebleminded persons a group of patients exhibiting an asymptomatic follicular hyperkeratosis scattered diffusely over the dorsum of the trunk but usually without involvement of the extensor surfaces of the extremities. Although various diagnoses have been considered from time to time, therapeutic measures attempted have proved futile. Recent intensive study of the 10 patients with this condition in the institution at the time of writing led us to the conclusion that we were dealing with an atypical manifestation of keratosis pilaris.

This group represents less than 0.5 per cent of the total number of patients in the institution. All the patients whose cases are reported were morons or imbeciles, but there was no correlation between the degree of mental deficiency and the intensity of the skin condition. We do not know whether this process is more frequent among feebleminded persons than in the population at large. In clinic and private practice during the past three years, however, we have observed but 1 patient, a 17 year old housemaid, who exhibited the changes described in this paper.

Although the ratio of females to males in the institution is 10.7 to 14.0, 7 females and 3 males composed the 10 patients studied. One might suspect a predilection for females, but our series seems too small to justify such a conclusion. All our patients were between the ages of 16 and 30, though it is likely that the process occurs at a much earlier age. From the history of 2 of the female patients (M. V. M. and M. M.) we were able to determine that the lesions had been present at the age of 8, at the time when the patients were admitted to the institution. In the other cases the parents and siblings of our patients were so widely distributed over eastern Pennsylvania that it was impossible to determine the time of onset or to obtain evidence of a familial tendency.

From the Department of Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania, Philadelphia, Herman Beerman, M.D., chairman, and the Pennhurst State School, Spring City, Pa., Thomas Butterworth, M.D., consultant in dermatology.

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In addition to mental deficiency, some of our patients exhibited neurologic manifestations. Spasticity was noted in 2 of them, while a third exhibited possible Wilson's disease (hepatolenticular degeneration). In 1 case there was a history of congenital syphilis; however, there was no evidence of current activity, and the serologic tests for syphilis had been giving negative reactions for several years. A search for tuberculosis failed to reveal evidence of that disease in this group. One of our male patients exhibited characteristics suggestive of feminism, although these features were not definite but suggested to us a trial of androgen therapy.

REPORT OF CASES

While the associated constitutional status of the patients varied greatly, the dermatologic manifestations followed a definite pattern. Representative of the entire group are the following cases, of 1 male and 2 female patients.

CASE 1.—S. U., a 31 year old man, a moron, had been a patient at the school since 1938. His physical examination revealed findings characteristic of right spastic hemiplegia, but various laboratory studies gave essentially normal results.

Over the back from the scapulas to the iliac crests he presented a bilaterally symmetric follicular erythematous papular eruption. The concentration of lesions was greatest over the supraspinatus areas, along the vertebral borders of the scapulas and in the mesial infrascapular regions. The pilosebaceous orifices surrounded by an erythematous halo were hyperkeratotic. Always asymptomatic, the lesions failed to show seasonal variation.

CASE 2.—M. V. M., a 26 year old imbecilic to moronic girl, was admitted to the institution in 1931 at the age of 8. At that time she showed bone changes and serologic evidence of congenital syphilis. Following antisyphilitic therapy there was reversal of the serologic reaction which had been maintained for more than ten years. Routine laboratory tests and the general physical examinations yielded no significant findings.

On admission and since that time persisting without major change, there was a bilaterally symmetric asymptomatic follicular erythematous punctate eruption over the back and shoulders. Not all the follicles were involved, but a greater concentration of lesions was present over the scapulas, with a decrease in number over the lower posterior portion of the thorax and lumbar regions.

CASE 3.—M. M., a 17 year old imbecile, entered Pennhurst in 1940 at the age of 8 years. She had had the usual childhood diseases and had been epileptic for an indefinite time. A general physical examination and laboratory studies revealed no contributory data.

Bilaterally and symmetrically situated over the back and shoulders was a follicular erythematous punctate eruption. The lesions were concentrated most over the supraspinatus areas, along the vertebral borders of the scapulas and in the infrascapular regions. Each follicle involved contained keratinous material and was surrounded by a red halo. The skin between the lesions was of unusually fine texture. The eruption was asymptomatic; over a period of years, it had shown no noticeable seasonal variation.

CLINICAL FEATURES

Nine of our 10 patients exhibited a bilaterally symmetric follicular erythematous macular to punctate or papular eruption on the back (fig. 1) from the level of the spinous process of the seventh cervical vertebra

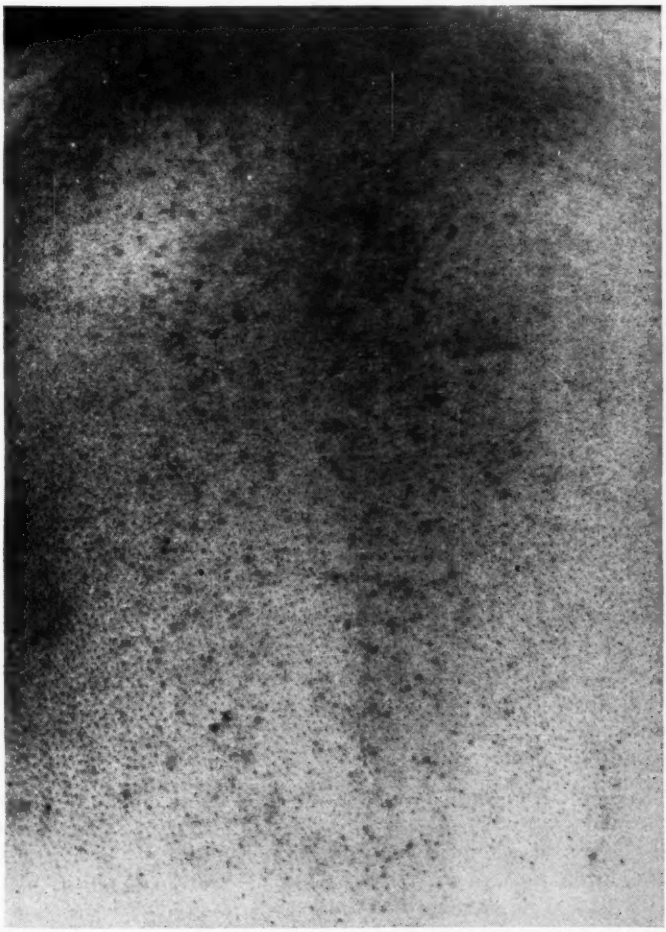

Fig. 1.—Follicular hyperkeratotic puncta surrounded by erythema distributed over the back.

to the top of the intergluteal cleft and laterally to the posterior axillary lines. The number of follicles involved varied. As a rule, a greater concentration of lesions occurred over the vertebral borders of the

scapulas and supraspinatus areas, with a decrease in the number of follicles involved in the interscapular region and costovertebral angles. Thus the distribution of changes may be said to have been greatest in areas most subject to pressure. The striking feature, however, was the lack of involvement of the lateral aspects of the deltoid regions, the arms, the lateral aspects of the buttocks and the thighs.

The tenth patient presented the usual distribution previously described but in addition exhibited similar lesions on the deltoid regions, arms and thighs. This fortuitous observation suggested a linkage of our other cases with an already well established clinical entity, namely keratosis pilaris. Subsequent histologic studies have seemed to justify this conclusion.

Considering the characteristics of the individual lesions, one finds that the follicular reaction varied considerably. About some follicles there was only a pinpoint erythema. Surrounding others were punctate erythematous papules filled with keratinous material and occasionally pierced by a lanugo type hair. The erythematous elements were more striking than the follicular plugging. Consistent with this observation, the lesions were soft to the touch and failed to impart the nutmeg grater–like roughness frequently found in the common forms of keratosis pilaris. The individual lesions persisted indefinitely, causing no subjective symptoms and exhibiting no seasonal variation.

PATHOLOGY

Since there were differences in the character of the individual lesions, typical specimens were excised and submitted to Dr. Herman Beerman for histologic examination. The epidermis of the average lesion showed some irregularities of the surface with slight hyperkeratosis but was otherwise normal. A mild but fairly deep follicular hyperkeratosis was observed (fig. 2). There was a low grade to moderate perivascular and perifollicular lymphocytic infiltration (figs. 2 and 3) with moderate edema of the upper portion of the cutis. No changes, however, were noted in the sweat or sebaceous glands or the subcutaneous fat.

Similar changes were noted in a specimen removed from the upper part of the arm of the patient with the transitional case who presented lesions in the usual areas of involvement of keratosis pilaris as well as on the back. In addition, there was hyperplasia of the fibers of the arrectores pilorum muscles in this section. It may be emphasized, however, that follicular hyperkeratosis and varying degrees of round cell inflammation were constant in all specimens excised and that there was no basic difference between the lesion on the arm of the patient with the transitional case and the specimens taken from the backs of the other patients.

Fig. 2.—Moderate hyperkeratosis of the follicle with perifollicular and perivascular lymphocytic infiltration.

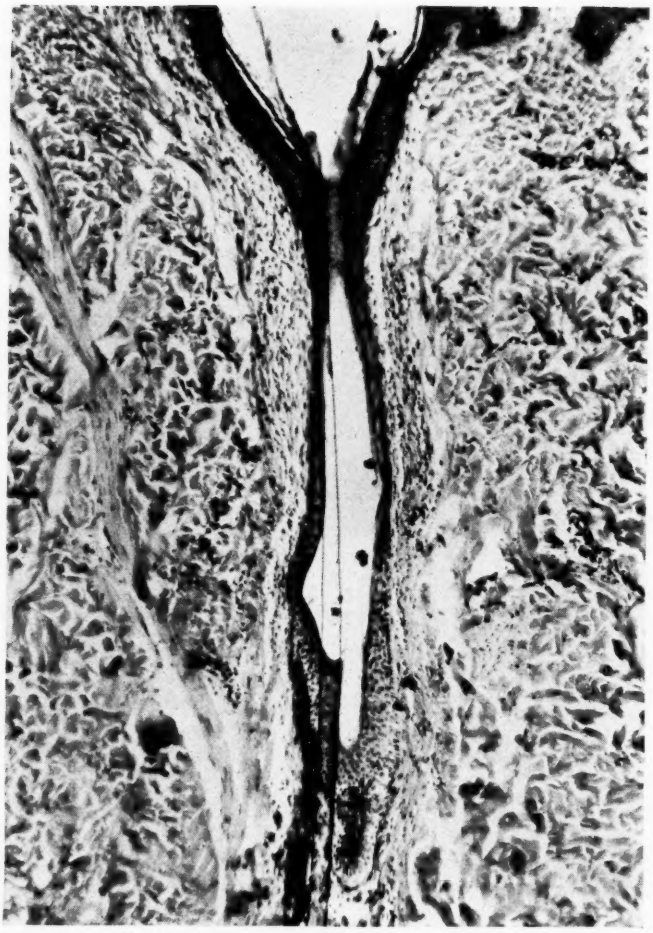

Fig. 3.—Follicular involvement of a very mild degree.

ETIOLOGY

We were unable to reach a definite conclusion as to the cause of this cutaneous process. The concentration of the lesions along the vertebral borders of the scapulas and supraspinatus areas suggests an irritation factor possibly from clothing or the contact of the projecting parts of the back with hard, flat surfaces. The perivascular and perifollicular lymphocytic infiltration raises the possibility that the process is inflammatory in origin with at least one of the causative factors endogenous. On the other hand, the granulomatous reaction seen in 1 of the cases was even suggestive of a tuberculid.

The presence of follicular hyperkeratosis usually raises the question of a possible vitamin A deficiency. We were unable to substantiate this possibility clinically or histologically. The diet of our patients had been adequate in all respects; the administration of supplemental vitamin A in doses of 200,000 units daily by mouth and 200,000 units intramuscularly twice a week for seven to twelve months did not affect the appearance of the disease. Montgomery [1] stated that spongiosis of the epidermis with vacuolization of the prickle cells or shriveling of the nuclei of the epidermal cells is suggestive of vitamin A deficiency, but we were unable to find evidence of such changes in our sections.

DIAGNOSIS

The presence of asymptomatic, relatively fixed pinpoint-sized to pinhead-sized erythematous follicular macules and of punctate papules limited to the dorsal surface of the trunk without grouping, seasonal variation, tendency to appear in crops or change in perspiration serves to differentiate our group of cases clinically from those of other follicular and keratotic processes. Follicular seborrheic dermatitis is accompanied with greasy yellowish scales on the scalp and patchy involvement of the postauricular, nasolabial, sternal and axillary regions. In cutis anserina, the papules, due to sudden chilling or emotional stress, are evanescent and quickly disappear when the exciting cause is removed. Phrynoderma is characterized by hyperkeratotic follicular plugging, and accompanying signs of vitamin A deficiency such as night blindness and keratomalacia are usually present. Response to proper vitamin therapy is usually prompt.

As a rule, lichen scrofulosus occurs in children who have tuberculosis of the bones or lymph nodes. It is characterized by groups of pinhead-sized or smaller reddish brown or flesh-colored slightly desquamating papules. The follicular syphiloderm is often distinctly annular or corymbiform, has a more acute course and is accompanied with other

1. Montgomery, H.: Inflammatory Dermatoses, in Syllabus of Dermal Pathology, Washington, D. C., Registry Press, 1948, pp. 17-18.

evidence of syphilis. In lichen spinulosus, a disease chiefly of children, there are minute filiform spines which protrude from acuminate follicular papules that are distributed symmetrically on the trunk and extremities. Its sudden appearance in crops and its spontaneous involution are distinctive. Pityriasis rubra pilaris is characterized by small follicular papules and disseminated erythematous scaling patches. The papules are topped by a central horny plug containing an embedded hair. The backs of the fingers, sides of the neck and extensor aspects of the limbs are frequently affected.

There remains for consideration the relation of our cases to keratosis pilaris. This disease is characterized by the presence of follicular convex or acuminate pinhead-sized or slightly larger papules usually distributed evenly on the anterolateral and posterolateral aspects of the arms and thighs. Rarely, the process may be generalized. If the hyperkeratotic elements predominate, the papule is grayish white (keratosis pilaris alba, Brocq,[2] but if, on the other hand, the inflammatory elements overshadow the keratotic, then the papules appear various shades of red (keratosis pilaris rubra, Brocq). Visually, the involved areas suggest "goose flesh", but, where hyperkeratosis is a prominent feature, a nutmeg grater–like sensation is imparted to the touch. The individual papule is often pierced by a hair either lanugo-like, broken off at the apex of the papule or curled within the lesion.

Keratosis pilaris may occur at any age though it is commonest in adolescence. Some of the affected persons have dry skin, and, in keeping with this characteristic, the process is more pronounced during the winter months. Moderate itching is observed in a few patients.

The histologic picture in keratosis pilaris is essentially a hyperkeratosis about the orifices of the pilo-sebaceous follicles. The follicular openings are widened, deepened and filled with a horny plug in which one or more fine hairs may be coiled. In the corium a moderate dilation of the vessels and some cellular infiltration are present. Atrophy of the sebaceous glands and of the arrectores pilorum may occur.

Follicular hyperkeratosis and perivascular and perifollicular lympocytic infiltration dominated the histologic picture in our cases, whereas clinically the erythematous elements overshadowed the hyperkeratotic. Because of the presence of small macules and punctate erythematous papules our cases resemble the keratosis pilaris rubra type of Brocq. The nutmeg grater–like sensation is lacking, the lesions actually being soft to the touch. The absence of seasonal variation, dry skin and itching are differences from the common type of keratosis pilaris of which we have omitted an explanation.

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2. Brocq, L.: Notes pour servir à l'histoire de la kératose pilaire, Ann. de dermat. et syph. **1**:25-37; 97-133; 222-238, 1890.

TREATMENT

All our therapeutic efforts have been futile in altering the clinical picture of our cases. The administration of resorcinol, salicylic acid, ammoniated mercury and sulfur in varying concentrations and vehicles afforded no relief. The application of wool fat U. S. P. under a cellophane® occlusive dressing for four weeks did not affect the appearance of the disease. Ultraviolet irradiation, while causing abundant peeling, failed completely to influence the disorder.

The use of internal remedies was also worthless in our hands. Large doses of vitamin A given parenterally and by mouth, with and without thyroid and ox bile extract, failed to alter the disease in any way. Administration of the vitamin B complex, orally and by injection, and of testosterone (in 2 male patients) was also without value.

SUMMARY

A report on a group of 10 cases exhibiting an asymptomatic symmetric follicular keratosis scattered diffusely over the dorsal surface of the trunk is presented. The outstanding features histologically were follicular hyperkeratosis and perivascular and perifollicular lymphocytic infiltration. Because of the presence of small macules and punctate erythematous papules, the cases are considered examples of keratosis pilaris rubra of Brocq with an atypical distribution. Therapeutic attempts have failed to alter the course of the disease.

80 Hanson Place.

HYPOALLERGENIC PENICILLIN IN OIL

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IN AN EARLIER paper, one of us (S. W. S.) reported[1] on the use of a combination of an antihistaminic drug and penicillin in an attempt to decrease the allergic responses to the antibiotic. Crystalline potassium penicillin G was dissolved in an isotonic solution of sodium chloride to which had been added 5 mg. per cubic centimeter of doxylamine (decapryn®) succinate (2-[α-(2-dimethylaminoethoxy)-α-methylbenzyl] pyridine succinate). Each cubic centimeter of this preparation contained 100,000 units of penicillin and 5 mg. of the antihistaminic drug. In a series of 292 patients, the reaction rate with the use of this doxylamine-penicillin mixture was 2.4 per cent, while in 400 control patients receiving the same aqueous crystalline penicillin alone, the rate was 6.5 per cent. As far as could be determined, the addition of the antihistaminic drug caused no loss in the efficacy of the penicillin or were blood levels any different. Patients previously reacting to plain penicillin were able to tolerate the doxylamine-penicillin mixture without reaction in almost every instance. Various cases were cited to show the efficacy of the combination, including those of 3 persons with syphilis whose treatment with procaine penicillin had been interrupted because of severe penicillin urticaria or erythema multiforme. Each of these received 600,000 units of the aqueous doxylamine-penicillin mixture daily for fifteen days (a total of 9,000,000 units) without the appearance of allergic manifestations. Since the writing of that paper, 8 other patients with syphilis have been treated with the aqueous doxylamine-penicillin mixture with good therapeutic results and without reaction. Many other patients with penicillin dermatoses severe enough to cause discontinuance of the drug were immediately switched to doxylamine-

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the results of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Simon, S. W.: Hypo-Allergic Penicillin, Ann. Allergy **8**:194 (March-April) 1950.

penicillin therapy and were able to complete the course of therapy while the skin lesions cleared. Therefore, with acceptance of the fact that the efficacy of the doxylamine-penicillin combination is not in question, a major disadvantage in the use of penicillin has been overcome if the reaction rate is decreased.

While aqueous penicillin is very effective, because of its instability and the necessity for refrigeration its use has been limited, for the most part, to hospitalized patients. Not wishing to enter into the discussion as to whether high sustained blood levels are better than high peak levels, we shall merely comment that the swing recently has been to prolonged penicillin levels. The most widely used preparation, at present, is procaine penicillin in an aqueous or oil base. Few percentage figures are available for reactions to this combination, but those reported vary from 0.2 per cent, given by Thomas, Rein and Kitchen,[2] to 1.4 per cent, by Lepper and his associates,[3] to 2.5 per cent, by Scott.[4] These figures seemed so low, considering that an additional source of sensitivity (procaine) had been added to the already potent sensitizer, penicillin, that we decided to observe a control series of our own. We did not attempt to separate those receiving procaine penicillin in aqueous solution from those receiving it in an oil base. In 175 patients receiving procaine penicillin in amounts ranging from one injection of 300,000 units to as much as 20,000,000 units in multiple injections there were skin reactions in 15, or 8.6 per cent.

To get a preparation along the lines of the aqueous doxylamine-penicillin combination we had a suspension prepared containing crystalline potassium penicillin G (300,000 units in each cubic centimeter of sesame oil), 15 mg. of doxylamine (oil-soluble base, not the succinate) and 2 per cent aluminum monostearate.[5] With this preparation, we found injections to be practically painless because of the anesthetic action of the antihistaminic drug. At no time did we encounter the common side reactions which accompany the oral administration of antihistaminic preparations. The penicillin is stable, and acceleration experiments have proved little loss of potency after one year at room tem-

2. Thomas, E. W.; Rein, C. R., and Kitchen, D. K.: Experiences with Single and Multiple Treatment Schedules of Early Syphilis with Procaine Penicillin in Oil and Aluminum Monostearate, Am. J. Syph., Gonor. & Ven. Dis. **33**:523 (Nov.) 1949.

3. Lepper, M. H.; Dowling, H. F.; Robinson, J. A.; Stone, T. E.; Brickhouse, R. L.; Caldwell, E. R., Jr., and Whelton, R. L.: Studies on Hypersensitivity to Penicillin: I. Incidence of Reactions in 1303 Patients, J. Clin. Investigation **28**:826 (Sept.) 1949.

4. Scott, V.: Semi-Weekly Treatment of Syphilis with Procaine Penicillin in Oil, J. Lab. & Clin. Med. **34**:998 (July) 1949.

5. The components were supplied through the courtesy of the Wm. S. Merrell Company, Cincinnati.

perature. Packaged in 10 cc. rubber-capped vials, the preparation is always available and may be washed from a syringe and needle without any special solvents. Penicillin blood levels were similar to those obtained with the use of the oil and wax preparations (Romansky).

We have used this preparation widely and to the time of writing (March 1950) in over 70 patients without reaction. Six of the 15 patients who reacted to procaine penicillin were switched to doxylamine and penicillin in oil with the same dosage without reaction.[5a]

Several persons with asthma were included in the series of 70 patients. The mixture of doxylamine and penicillin in oil did not aggravate or produce any asthmatic attacks. Since therapy was required for control of various infectious diseases, no opportunity presented itself for evaluating the possible beneficial effects of the combination on asthma.

Ten patients with syphilis of the central nervous system and 1 patient with a gumma of the skin were treated. In addition, among the 10 patients with either tabes dorsalis, dementia paralytica or the tabetic form of dementia paralytica, several had primary optic atrophy and one had an aneurysm of the aorta. Most of these patients had previously been treated with penicillin. Quantitative serologic tests for syphilis when made prior to and after therapy with the doxylamine-penicillin mixture revealed a general tendency toward lowering of the quantitative serologic titer. Follow-up examination of the spinal fluid was made in 1 patient, and two months after therapy there was a decrease to normal of the cell count and a corresponding decrease in the total protein.

One patient with asymptomatic syphilis of the central nervous system had twelve months previously reacted to the topical use of penicillin ointment with a contact dermatitis. Four months later he received procaine penicillin for his syphilis, and after twelve daily injections of 300,000 units each he reacted with severe urticaria, angioneurotic edema and an id type of papulovesicular dermatitis. Eight months later, he was given 300,000 units of doxylamine and penicillin in oil daily for fourteen days without the appearance of allergic manifestations.

Another patient with latent syphilis was given seven daily doses of 200,000 units of aqueous procaine penicillin for prophylaxis before ocular surgery. Nine days later he acquired a wheal-like eruption of the scalp and coccyx associated with pronounced pruritus. Tripelennamine (pyribenzamine®), 50 mg. three times a day was prescribed but discontinued the following day when symptoms were more pronounced and accompanied with swelling of the throat and some dysphagia, and

5a. Others have reported to us (July 1950) that in the use of this preparation in over 200 additional patients, many of whom had reacted previously to other types of penicillin, no reactions were observed.

edema of the hands, fingers and feet. Doxylamine was substituted for the tripelennamine in 25 mg. doses, but the patient was not relieved until he had been given two intravenous injections, each of 1 mg. of histamine base in 250 cc. of saline solution. The aqueous doxylamine-penicillin mixture was given in a dose of 300,000 units on the twentieth day after the development of the urticaria. No objective signs were seen, but the patient complained of slight chills, swelling of the tongue and throat, generalized pruritus and pain in the chest. Therapy with the doxylamine-penicillin combination was stopped, and immediately treatment with doxylamine and penicillin in oil, 300,000 units daily was begun. This was increased from one to four injections daily, and the patient received 5,100,000 units over a six day period, asymptomatically.

COMMENTS

Sensitivity to penicillin has been repeatedly stressed, particularly in those persons taking large doses over a considerable period or several courses of treatment with the antibiotic. Recommendations regarding the prevention and treatment of these reactions are numerous.[6] The introduction of procaine penicillin has in no way changed the problem. We are too commonly faced with these reactions and incapacitations arising from the use of this valuable antibiotic medication. Now, it is felt, something concrete can be offered to decrease the frequency of these distressing allergic manifestations.

It is not our intention to propose schedules or dosages for the treatment of syphilis. We are primarily interested in decreasing to a minimum the allergic reactions associated with penicillin therapy.

Few observations on reaction rates from procaine penicillin are available because of the short time this preparation has been in use. It is our opinion that when reliable reaction rate data are made known the rates will be observed to be at least as high as those with crystalline penicillin.

The treatment of penicillin reactions after they develop, even with means including the administration of antihistaminic drugs and histamine intravenously, is at best unsatisfactory. Prophylaxis using orally administered antihistaminic preparations has never been very successful.

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6. Beerman, H.: Drug Eruptions: A Survey of Recent Literature, Am. J. M. Sc. **218**:446 (Oct.) 1949. Feldman, M. D.: Sensitization to Penicillin: The Types of Reactions; Therapy and Prevention, Ohio State M. J. **45**:131 (Feb.) 1949. Pillsbury, D. M.; Steiger, H. P., and Gibson, T. E.: The Management of Urticaria Due to Penicillin, J. A. M. A. **133**:1255 (April 26) 1947. Tucker, H. A.; Mohr, C. F.; Hahn, R. D., and Moore, J. E.: Syphilis: A Review of the Recent Literature, Arch. Int. Med. **83**:238 (Feb.) 1949.

So far as we have been able to try the new combination of doxylamine and penicillin, we have been impressed with the lack of reactions. It is our desire that more investigators try it; only then will we be sure that there is a hypoallergenic form of penicillin.

SUMMARY AND CONCLUSIONS

A report on the use of doxylamine and penicillin in oil in the treatment of over 70 patients with various infections, including syphilis, is presented. The combination of aqueous doxylamine and penicillin had previously been proved efficacious as a therapeutic agent and less hazardous in its tendency to produce aliergic manifestations. Apparently doxylamine and penicillin in oil is superior even to the aqueous solution in preventing reactions to penicillin.

Clinical Notes

INFLUENCE OF GRENZ RAYS ON HISTAMINE-INDUCED MANIFESTATIONS

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FREDERICK BLANK, M.D.
AND
IRVING H. DISTELHEIM, M.D.
NEW YORK

The search for an antihistaminic agent has been most intense in the past few years. At the time of writing there are in the neighborhood of fifteen different preparations on the market, this situation giving an indication of the amount of work that has been done by individual laboratories. However, the preponderance of research is directed toward finding a chemical agent which will combat or compete with the effect of histamine regardless of the shock organ, be it the bronchi, the nasal mucosa, the skin or another. That there might be physical means of releasing or forming antihistaminic substances in the skin seemed plausible after the observation of a number of cases of asthmatic episodes (and other conditions in which a histamine action is probable) in which the condition was relieved and stayed relieved for months, after indirect or general radiation of several areas of skin surface with grenz rays. There is also a remarkable coincidence of indications for antihistaminic drugs and general grenz ray therapy. This point was considered in view of previous work showing that there can be local sensitization (with possible release of histamine) to grenz rays.[1] As the biologic effect of radiation, especially as regards chemical substances released, is for the most part still an enigma, just what the mechanism involved might be is only hypothetic.[2]

MacKee and Cipollaro[3] stated that all biologic changes in tissue doubtless result from chemical changes produced in the living cell. There are, of course, other intermediate changes, of which ionization is a basic process. Grenz rays belong to the ionizing radiations. Physically they differ from ordinary roentgen rays by their lack of penetration power and their photoelectric effect. Rays of about 2 angstrom units are practically entirely absorbed in the skin and do not penetrate more deeply than the subcutaneous layer. This fact demonstrates that any physiologic manifestation must originate in these layers and not in deeper organs, and thus grenz rays are rendered especially fit for the experiment in question.[4]

From the Department of Dermatology and Syphilology, New York University—Bellevue Medical Center, service of Dr. Frank C. Combes.

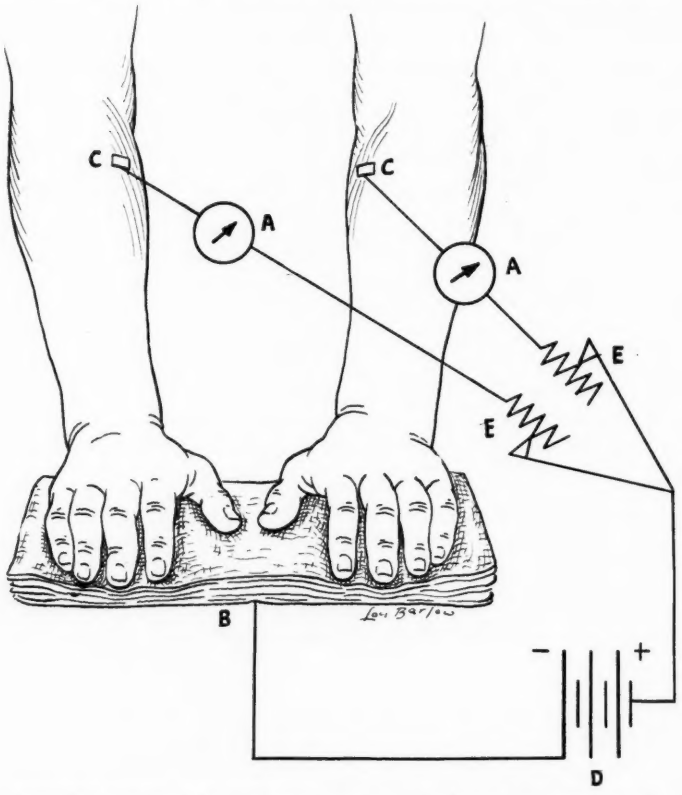
1. Oppenheim, M.: Local Sensitization of the Skin to Grenz Rays by Bergamot Oil, J. Invest. Dermat. **8**:255 (May) 1947.

2. Ellinger, F.: The Biologic Fundamentals of Radiation Therapy: A Textbook, translated by R. Gross, New York, Elsevier Pub. Co., 1941.

3. MacKee, G. M., and Cipollaro, A. C.: X-Rays and Radium in Treatment of Diseases of the Skin, ed. 4, Philadelphia, Lea & Febiger, 1946.

4. Bucky, G.: Grenz Ray Therapy, translated by W. J. Highman, New York, The Macmillan Company, 1929. Gertz, W.: Versuche einer Beeinflussung des Ulcusleidens mittels Grenzstrahlen, Strahlentherapie **32**:489, 1929. Schilling, E.: Die Sensibilisierung des vegetativen Systems durch Buckysche Grenzstrahlen, Ztschr. f. d. ges. exper. med. **74**:713, 1930. Denier: Action thérapeutique des rayons de Bucky sur les visceralgies, Rev. d'actinol. **6**:612, 1931. Ebbehøj, E.: Untersuchungen über ultraweiche Röntgenstrahlen, Copenhagen, Nyt Nordisk Forlag, 1937.

One may assume, however, that the substance liberated, if such an effect actually occurs, is somewhat different in content and mode of action than the enzymic histamine which has been shown to lack an inhibiting effect in the living animal and any specific effect in allergic conditions.[5] Best and McHenry's [6] conclusion that histaminic substances have no effect on the antigen-antibody reaction is still to be answered. In the light of the present day moderate efficacy of



Apparatus employed in the experiments. *A* indicates the ammeter; *B*, the negative electrodes; *C*, the positive electrodes; *D*, the source of galvanic current, and *E*, the resistors.

the histamine antagonists, it was supposed that another similar substance and substances might be liberated. It was also believed that these could be produced by indirect irradiation or that the substances produced locally could circulate

5. Feinberg, S. J.: Histamine and Antihistaminic Agents, J.A.M.A. **132**:702 (Nov. 23) 1946.

6. Best, C. H., and McHenry, E. W.: A Note on Histaminase, Canad. M.A.J. **43**:163 (Aug.) 1940.

and produce systemic effects. Therefore a series of experiments were set up, as will be discussed in this paper, to determine whether grenz irradiation substituted for the administration of histamine antagonists would have a similar effect.

METHOD

After the method of Cohen and Friedman [7] a dilution of histamine diphosphate (1:6,400,000) was prepared. The inner surfaces of the forearms were employed, and the histamine solution was introduced by iontophoresis. The electrodes were made of tin in 1 square centimeter dimensions and placed over 1 square centimeter of filter paper saturated with the histamine solution. Since comparative studies were made, the electrodes of the right and left arm (irradiated and nonirradiated) were both connected to the positive pole (see figure). However, to avoid any inaccuracies in iontophoretic delivery to each arm, an ammeter was introduced into each branch of the positive pole, a constant check thus being afforded. In these experiments 0.8 milliamperes of direct current was employed for three minutes. A 4 by 8 inch (10 by 20 cm.) gauze bandage soaked in a 10 per cent sodium chloride solution was attached to the negative pole for completion of the circuit.

Surprisingly, after a series of preliminary experiments, the most pronounced irradiation effect was not immediately after irradiation, but delayed its appearance from four to six hours. Therefore the volar aspect of one forearm was irradiated with 300 r of grenz rays (half-value layer of 25 microns of aluminum and 15 milliamperes) four to six hours before the introduction of the histamine solution. Readings after the histamine introduction were taken immediately; after twenty minutes, after six hours and after twenty-four hours. The history of any allergies in the subjects or their families was carefully noted.

RESULTS

Forty subjects were treated in the manner described. Of these, 22 showed definite increased reactions to histamine on the irradiated side, 8 showed more intense reactions on the nonirradiated side and 10 gave an equivocal response. These data were further broken down to show that of the 22 increased reactions on the irradiated side, 5 were manifested by increased whealing, 7 by increased erythema and 10 by both increased whealing and erythema. On the nonirradiated side, of the 8 more intense reactions, 5 were evidenced by increased whealing, 1 by increased erythema and 2 by both increased erythema and whealing. In the 10 cases with equal results, there was no whealing without erythema; and thus 6 cases showed erythema alone, and 4, both whealing and erythema of equal dimensions. Seven subjects either had a history of allergies themselves or had family histories of allergies. Of these, 6 showed an increased reaction on the irradiated side (see tables 1 and 2).

COMMENT

There are several questions which this work has attempted to answer. First, do grenz rays exert any antihistaminic effect? The observations in the experiments described answer this in the negative. Second, what are the possible explanations for the increased histaminic effect observed in the experiments reported? Of prime consideration is the possibility of an increase of histamine released, which might

7. Cohen, M. B., and Friedman, H.: Immunity Against H-Substance, J. Allergy **15**:245 (July) 1944.

explain the desensitization noted in persons with asthma who have been subjected to repeated generalized grenz irradiation. This observation is reminiscent of the reports of desensitization effected by the repeated administration of small amounts of histamine. Also to be considered is the possibility of the release of a substance which acts as a nonspecific desensitization agent or antigen. Then, too, there is the possibility of a purely physical vasomotor reaction to the irradiation, namely vasodilation augmenting the flare and edema observed. The prompt reaction in allergic persons appears significant.

TABLE 1.—*Reactions to Administration of Histamine Diphosphate After Grenz Irradiation*

	More Intense on Irradiated Arm	More Intense on Nonirradiated Arm	Equal on Both Arms
Whealing	5	5	0
Erythema	7	1	6
Whealing and erythema	10	2	4
Total number of reactions	22	8	10

TABLE 2.—*Increased Effects Noted in Seven Patients With Histories of Allergy*

	Erythema	Whealing	Whealing and Erythema	Total No. of Reactions
Irradiated side	1	1	4	6
Nonirradiated side	1	0	0	1
Total	2	1	4	7

CONCLUSIONS

Twenty-two, or 55 per cent, of 40 subjects showed an increased local reaction to histamine after grenz irradiation. Eight, or 20 per cent, showed a decreased local reaction to histamine after grenz irradiation. In 10, or 25 per cent, the responses were equivocal. An interesting observation was that of the increased reactivity to histamine after irradiation in 6 of the 7 patients with allergic backgrounds.

The results tended to disprove the original contention that local grenz irradiation produced any antihistaminic substances locally. Whether indirect irradiation will produce such substances will have to be determined in later experiments.

Society Transactions

MINNESOTA DERMATOLOGIC SOCIETY

Fred T. Becker, M.D., *President*
E. T. Ceder, M.D., *Secretary*
Jan. 28, 1949

Pemphigus Foliaceus. Presented by DR. CARL LAYMON, Minneapolis.

Epidermolysis Bullosa Hereditaria. Presented by DR. CARL LAYMON, Minneapolis.

A Case for Diagnosis: Dermatitis Herpetiformis? Presented by DR. CARL LAYMON, Minneapolis.

DISCUSSION OF PRECEDING CASES

DR. CARL LAYMON, Minneapolis: Several months ago the woman with the pemphigus foliaceus presented classic lesions of the Senear-Usher syndrome. Dr. Senear has stressed that this type of pemphigus may be extremely slow in its course.

DR. HERBERT RATTNER, Chicago (by invitation): Another point that Dr. Senear mentioned was that in many cases the Senear-Usher syndrome eventually develops into pemphigus foliaceus rather than pemphigus vulgaris, and I think this case is an example of that.

DR. PAUL A. O'LEARY, Rochester, Minn.: In the case for diagnosis (dermatitis herpetiformis?), I suggest the diagnosis of morphea with bullae in preference to dermatitis herpetiformis. The patient has not had cutaneous sclerosis at any time, but the atrophic and pigmented plaques suggest morphea. However, I could not associate the bullous lesions about the mouth with morphea. Pruritus, according to the patient's story, was conspicuous by its absence.

DR. FRED T. BECKER, Duluth, Minn.: Two patients we have seen with erythema multiforme with herpes simplex lesions demonstrated the virus in erythema multiforme that we most frequently associate with recurrent herpes simplex.

Lichen Sclerosus et Atrophicus. Presented by DR. CARL LAYMON, Minneapolis.

Mrs. A. E. F., a 57 year old housewife, noted a pruritic macerated eruption of the vulva and intergluteal regions in the spring of 1948. Gynecologic examination revealed no abnormalities.

Therapy with premarin® (estrogenic substances [water soluble]) cream and superficial roentgen radiation was initiated in June 1948. Pronounced improvement in the eruption was manifest in three and a half months.

DISCUSSION

DR. UDO WILE, Ann Arbor, Mich. (by invitation): I am wondering whether the microscopic picture and the clinical picture wouldn't fit almost as well for an extensive kraurosis as for lichen sclerosus et atrophicus. The lesion was so

extensive and there were no outlying smaller atrophic lesions which had developed about the genitalia. It is much commoner, of course, to find these on the back of the neck, wrists and shoulders. The microscopic picture showed atrophy, common to both kraurosis and lichen sclerosis.

DR. ASHTON WELSH, Cincinnati (by invitation): Recently I saw 2 interesting patients who had lichen sclerosus et atrophicus. The first patient had generalized typical lichen sclerosus et atrophicus. On the arms where the original lesions had appeared there were changes almost like poikiloderma. There was hyperpigmentation, considerable atrophy and spotty telangiectasia. The other lesions were those of typical lichen sclerosus et atrophicus except over the abdomen where raised whitish nodules which looked like blisters were present. Repeated biopsies of specimens including the nodules on the abdomen revealed a histologic picture typical for lichen sclerosus et atrophicus. The other patient had typical lesions of lichen sclerosus et atrophicus involving almost the entire thorax and both arms. Both cases were remarkable because of the extensive character of the eruption. I think that in the patient presented here the extensive distribution over the genitals, groin and perineal and perianal areas favors the diagnosis of lichen sclerosus et atrophicus and rules against kraurosis, in which the atrophic change is usually limited to the inner surfaces of the labia.

DR. FRED T. BECKER, Duluth, Minn.: I should like to emphasize again what Dr. Laymon has said regarding the great similarity of these two conditions in the male and the female. In Chicago recently, several cases were presented of female patients whose lesions were benefited from the use of estrogenic ointments. We might try giving the men testosterone.

Chronic Discoid Lupus Erythematosus: Six Cases. Presented by DR. CARL LAYMON, Minneapolis.

DISCUSSION OF CASES OF LUPUS ERYTHEMATOSUS

DR. PAUL A. O'LEARY, Rochester, Minn.: The man with the extensive disseminated lesions said that last fall he was given tocopherols and that the lesions cleared up and he was quite free from them for about four months following that therapy.

DR. STEPHEN ROTHMAN, Chicago (by invitation): So far my associates and I have had only 1 patient who responded remarkably well to treatment with mixed tocopherols. This was a woman with a case of chronic intensely infiltrated lupus erythematosus refractory to all other treatments over an observation period of twelve years.

DR. UDO WILE, Ann Arbor, Mich. (by invitation): I am beginning to wonder whether there may be some climatologic element in the incidence of erythematosus lupus of the discoid variety, because I am tremendously impressed with the number of cases you have here. The population of the Twin Cities is somewhat less than that of Detroit, and my associates and I don't see anywhere near the amount of discoid lupus erythematosus in our clinics that you see here. Do you actually see as many cases here as this group would seem to indicate?

DR. CARL LAYMON, Minneapolis: It seems to me, and I think to all of us, that we see more in this part of the country than is seen in other parts.

DR. H. E. MICHELSON, Minneapolis: I feel sure there is hardly a time when we haven't some acute lupus erythematosus in one of the hospitals, and the chronic type is constantly observed. It is interesting to note that, according to Spitzer,

in Breslau there were more cases of lupus vulgaris reported than of lupus erythematosus, with a ratio of 2 to 1.

DR. STANLEY E. HUFF, Minneapolis (by invitation): My associates and I studied the circulation of the fingers of patients with chronic lupus erythematosus and found definite abnormalities both in the plethysmogram and in the reflex hyperemia. The plethysmogram is quite characteristic and shows changes similar to those found in hypertension, arteriosclerosis and pseudoxanthoma elasticum. This observation would lead us to believe the chonic discoid type of lupus erythematosus is merely a manifestation of a generalized vascular disorder.

A Case for Diagnosis: Keratodermatitis Hypoestrogenica? Presented by DR. CARL LAYMON, Minneapolis.

DISCUSSION

DR. FRANCIS W. LYNCH, St. Paul: One may choose to hold either a narrow or a broad concept of the disorder presented by Dr. Laymon's patient. If one uses the term "keratoderma climactericum," one should probably require that the patient be in the climacteric and have arthritis, obesity and hypertension in addition to the characteristic eruption on the palms or soles or both. This patient presents all the required features. I do not hold to such a narrow concept and would accept many cases as belonging in this general group even though one or many of the aforementioned features may be absent. With this broader view it is necessary to regard the condition as a manifestation of neurodermatitis.

DR. CARL LAYMON, Minneapolis: The patient received no estrogenic therapy.

Pyoderma Gangrenosum. Presented by DR. CARL LAYMON, Minneapolis.

Miss L. B., a 22 year old office worker, first noted a pustular and ulcerating eruption on the right fifth toe in April 1947. Antibiotics were administered topically and parenterally during the summer of 1947 with temporary improvement. In the fall of 1947 pustules appeared on the feet, buttocks, vulva and arms. Ulcerations were present on the feet. She was hospitalized at the University and Abbott hospitals in November and December 1947 for study and therapy of suppurating inguinal lymphadenitis and septicemia. The general physical condition was normal except for anemia. No amebas or fungi were found. A roentgenogram of the lungs revealed normal conditions.

Ambulation produced an exacerbation of the pyoderma and ulceration. Sulfapyridine powder, lyocyte® powder (lyophilized human red blood cells) nitrofurazone (furacin®) ointment and chlorophyll ointment were administered with no definite improvement. The patient was again hospitalized in April and May 1948. Remission in symptoms was produced by surgical débridement and the application of compresses of aluminum acetate (Burow's) solution. A dyshidrotic eruption appeared when sulfonamides or penicillin was given. Streptomycin was administered parenterally and topically. Liver and vitamins were recently given parenterally, and bacitracin ointment was applied locally with indifferent results. There is no history of gastrointestinal disturbances.

Examination shows an indolent ulcer with central cicatricial healing and an advancing, undermined, purplish red, purulent border on the anterior and lateral surfaces of the left leg. The dorsal aspect of the left foot presents a cicatrix with an occasional pustule.

A histologic specimen was presented.

DISCUSSION

DR. STURE JOHNSON, Madison, Wis. (by invitation): Instead of using bacitracin topically, we have been injecting it subcutaneously into the edge of certain gangrenous lesions with excellent results. Bacitracin was found to be nephrotoxic, causing transitory casts and red and white blood cells in the urine. Pain from injection was controlled by dissolving 2,000 units of bacitracin in 1.0 cc. of a 2 per cent aqueous procaine solution. Of the various topical medicaments used, either alone or in combination with bacitracin, zinc peroxide was found to be the best.

DR. JOHN F. MADDEN, St. Paul: I think that this condition resembles the case of necrobacillosis reported by Dr. Maurice Reuter at the last meeting of the American Dermatological Association. Anaerobic cultures should be made according to the method outlined in Dr. Reuter's paper.

DR. STURE JOHNSON, Madison, Wis. (by invitation): Meleney and Johnson have isolated a microaerophilic streptococcus from many gangrenous ulcers and have obtained good results with the use of bacitracin.

DR. PAUL A. O'LEARY, Rochester, Minn.: I believe the term pyoderma gangrenosum should be limited to the entity we originally ascribed it to, namely a gangrenous ulceration of the skin in association with ulcerative colitis or some similar constitutional debilitating disease. At the moment, the discussion has been about two separate entities; since pyoderma gangrenosum is seen in association with debilitating diseases, usually ulcerative colitis or empyema, I believe this young woman either has ulcerative colitis or will manifest it in the near future because that observation has been made in practically all our cases of this type. Treatment directed to the colitis results in healing of the ulcerations, although recurrences of the colitis as well as of the ulcerations are common. These patients react unfavorably to most hypodermic injections, usually acquiring ulceration following injections of any sort.

DR. STURE JOHNSON, Madison, Wis. (by invitation): The etiology of ulcerative colitis may be bacterial, allergic or psychosomatic. Can pyoderma gangrenosum create a psychosomatic response which in turn causes gastrointestinal symptoms in those cases in which epidermal changes precede the gastrointestinal?

DR. UDO WILE, Ann Arbor, Mich. (by invitation): I should like to call attention to the fact that amebiasis of the skin would look very much like this particular case.

DR. CARL LAYMON: We have made repeated searches for amebas.

Squamous Cell Epithelioma: Two Cases on the Buccal Mucous Membrane. Presented by DR. CARL LAYMON, Minneapolis.

Recurrent Epithelioma of the Right Ear. Presented by DR. CARL LAYMON, Minneapolis.

Carcinoma of the Penis. Presented by DR. CARL LAYMON, Minneapolis.

Balanitis Xerotica Obliterans. Presented by DR. CARL LAYMON, Minneapolis.

Granuloma Annulare: Two Cases in Children. Presented by DR. CARL LAYMON, Minneapolis.

Necrobiosis Lipoidica Diabeticorum: Two Cases. Presented by DR. CARL LAYMON, Minneapolis.

A Case for Diagnosis: Macular Atrophy? Presented by DR. CARL LAYMON, Minneapolis.

Cavernous Hemangioma with Syndactylism and a Supernumerary Digit. Presented by DR. CARL LAYMON, Minneapolis.

Glomus Tumor (?). Presented by DR. CARL LAYMON, Minneapolis.

Sarcoidosis. Presented by DR. CARL LAYMON, Minneapolis.

Neurofibromatosis with Sarcomatous Degeneration. Presented by DR. CARL LAYMON, Minneapolis.

DETROIT DERMATOLOGICAL SOCIETY

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Feb. 16, 1949

Acrodermatitis Atrophicans Chronica. Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

DISCUSSION

DR. JAMES R. ROGIN: The lesions look more like poikiloderma on the arms; they are compatible with acrodermatitis on the legs.

DR. HERMANN PINKUS: This man presents the typical changes of acrodermatitis atrophicans chronica, and, like all the half dozen patients with the disease whom I have seen in the last fifteen years, he was born in Europe. This disease, which is so uncommon here, is not rare in the clinics of Germany, but I yet have to see a case in a native-born American. This circumstance has been puzzling to me for a long time because the disease is neither contagious nor hereditary, the patients afflicted with it in this country usually have lived here for many years, as this man has, and they don't bring the manifestations of the disease with them but acquire them at a later age. As far as treatment is concerned, local applications of thorium-X ointment are beneficial in the early inflammatory stage which this man presents on his upper extremities and at the upper limits of the involved skin on the thighs. Thorium-X can arrest the process and prevent the development of the atrophic stage.

DR. JAMES R. ROGIN: I didn't see thinning of the skin on the arms.

DR. FRANK MENAGH: The eruption on the arms came last summer, and atrophy is not pronounced yet in this relatively early stage.

DR. FRANK STILES: The atrophy, reticulation, pigmentation and teleangiectasis on the arms resemble the features in the description of poikiloderma. The eruption on the legs is compatible with acrodermatitis.

Calcinosis Cutis. Presented by DR. DAVID KAHN, Lansing, Mich.

A white housewife, aged 57, in 1946 first noted several round, whitish lesions the size of a pinhead which appeared to be localized thickenings of the skin of the tips of the left third and fifth fingers. Similar lesions later developed in the thumb. In some cases inflammation occurred, with subsequent breakdown of the overlying skin and the discharge of a creamy material containing chalky particles. The tips of all the fingers became bright red or livid and exhibited a firm, tender, persistent swelling. Nodules also appeared on the right palm and right knee and on the dorsum of the left foot.

There are occasional sharp shooting pains in the affected fingers, and pain on extending the metacarpocarpal joint of the left thumb. Occasional prickling sensations have occurred in hands and feet on the patient's arising in the morning since the menopause, seven years ago. The fingers blanch on exposure to cold. A goiter was removed in 1925. There is no history of excessive intake of vitamin D. The patient took a thyroid preparation for several months prior to the onset of the lesions.

The patient had measles, mumps, chickenpox and whooping cough as a child. All teeth were extracted in 1946 because of "pyorrhea." Her menopause came at

the age of 50. Two children are living and well. Her father died of cerebral hemorrhage, and her mother died at age 77 of gallstones. Three siblings have no lesions similar to the patient's. No familial diseases are known. The patient's blood pressure is 120 systolic and 80 diastolic. The posterior tibial and dorsalis pedis pulses are palpable bilaterally. Examination of the skin shows erythema and telangiectasia in rosacea areas. There is livid erythema and firm swelling of the terminal portions of the fingers. The ends of the left thumb and of the middle and fifth finger reveal hard subcutaneous nodules of varying size, some of which have broken down, with the discharge of chalky or creamy material containing gritty particles. There are grouped nodules over the palmar aspect of the right third metacarpophalangeal joint. The involved fingers did not blanch in cold tap water, but the patient asserts that they do so in cold air. A subcutaneous nodular plaque with peripheral discrete nodules with adherence to the skin is present over the right knee, and there are nodules along the extensor tendons of the dorsum of the left foot.

The results of laboratory examinations were as follows: serum calcium, 13.5 mg. (elevated); serum cholesterol, 250 mg. (normal), and blood uric acid, 3.1 mg. per hundred cubic centimeters (normal). The reaction to the Kahn test was negative; the blood count was within normal limits, and urinalysis showed a specific gravity of 1.005, with no pathologic substances. Biopsy of a specimen from a plaque on the right knee showed calcinosis cutis. Roentgenograms of the right knee and left hand showed dense masses in the soft tissue.

DISCUSSION

DR. ARTHUR CURTIS: Hyperparathyroidism must be ruled out in this case, for that condition may be a cause of calcium deposits in the skin.

DR. C. E. REYNER: Dr. Arthur P. James told me that he had obtained some good results in similar cases through the use of antuitrin®-S (an extract of the urine of pregnant women containing the pituitary-like gonadotropic factor).

Uveitis; Papulonecrotic Tuberculid; Erythema Nodosum. Erythema Induratum? Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

Scleroderma, en Coup de Sabre. Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

Scleroderma, en Coup de Sabre, in a Man Aged 22. Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

Linear Circumscribed Scleroderma. Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

Psoriasis; Arsenical Hyperkeratosis; Multiple Squamous Cell Epithelioma. Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

Dermatitis Herpetiformis: Two Cases. Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

Xanthoma Papulosum; Dermatitis Papillaris Capillitii. Presented by DR. EUGENE A. HAND, Saginaw, Mich.

Mycosis Fungoides. Presented by DR. HERMANN PINKUS for DR. LOUIS ZLATKIN.

Acne Aggregata Seu Conglobata. Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

Pseudopelade (Alopecia Cicatrisata); Seborrhea of the Scalp. Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

Pemphigus Vulgaris; Dermatitis Factitia (?). Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

Granuloma Annulare. Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

A Case for Diagnosis: Plantar Wart? Roentgen Dermatitis? Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

Acne Rosacea: Adenomatoid Hyperplasia of Sebaceous Glands. Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

A Case for Diagnosis: Onycholysis? Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

Lupus Erythematosus. Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

Tinea Versicolor; Pityriasis Rosea(?). Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

Lymphangioma Circumscriptum. Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

Rheumatic Fever? Liquefying Nodular Panniculitis (Shaffer)? Presented by DR. FRANK MENAGH and DR. C. E. REYNER.

Mycosis Fungoides? Phenolphthalein Eruption? Presented by DR. S. J. JOYCE.

A Case for Diagnosis: Parapsoriasis en Plaques? Presented by DR. HERMANN PINKUS.

C. H. Reiner, M.D., *Chairman*

Hermann Pinkus, M.D., *Recording Secretary*

March 27, 1949

All cases not otherwise noted were presented by Dr. A. C. Curtis and the Staff of the Department of Dermatology, University Hospital, Ann Arbor, Mich.

Cushing's Syndrome and Hidradenitis Suppurativa.

M. P., an unmarried white woman 50 years of age, was well until 1931, when suddenly her menses became scanty and irregular. Hirsutism of the face, trunk and extremities developed gradually, and it soon became necessary for her to shave daily. Approximately one year later her menses became regular but the flow was even scantier. Her voice became husky, and a fat pad gradually developed over the posterior portion of the neck. Severe headaches occurred at intervals of two to three months and would persist for two to three days. About this time she commenced having pustular lesions on the face, axillas, breasts and extremities and in the skin of the inguinal, perineal and pudendal regions. The lesions were relatively painless, hard, erythematous and persistent and when incised discharged a thick yellow-greenish fatty material with a rancid odor. Persistent sinuses would follow. From 1938 to 1942 the skin was relatively free of involvement, but the lesions recurred and have been present continuously since the latter date. Treatment with vaccines, sulfonamides, penicillin, an orally administered tin preparation and superficial roentgen radiation was ineffective. In November 1946 the patient was hospitalized and diagnoses of Cushing's syndrome, hidradenitis suppurativa and diaphragmatic hernia were made. In addition to local therapy to the skin, the patient received deep roentgen ray therapy to the pituitary gland (2,100 r) without noticeable improvement, although her headaches subsided. Shortly afterward her menses ceased. In the fall of 1947 the axillary skin was excised and the defect repaired with skin grafts. New pustular lesions continued to appear. The patient was admitted to the University Hospital March 22, 1949, for further treatment. She was not acutely ill. There was a dusky red color to the skin and pronounced hypertrichosis of the face, trunk and extremities. A "buffalo" type of fat pad was present on the posterior portion of the neck and upper part of the thorax. Incision scars were present in both axillas. The left breast was partially amputated, and in the remaining overlying skin was an indolent ulcer about 2 cm. in diameter. Similar lesions were present on the legs. The inguinal regions showed pustular lesions and discharging sinuses. The liver was enlarged and palpable about 10 cm. below the right costal margin; the spleen was enlarged and palpable about 5 cm. below the left costal margin. Both dorsalis pedis pulses were absent, and the posterior tibial pulses were barely perceptible. The blood pressure was 150 systolic and 100 diastolic.

The reaction to the Kahn test was negative. There was 16.7 Gm. of hemoglobin per hundred cubic centimeters. The red blood cell count was 8,500,000; the white blood cell count was 19,000, with a normal differential count. Cultures from skin lesions revealed only gram-positive cocci. Repeated smears and cultures for acid-fast organisms were negative. Urinary 17-ketosteroids were 14.1 mg. per day (normal, 7 to 10 mg. per day). The response in the glucose tolerance test was slightly prolonged but not abnormal. Biopsies of skin tissue showed active purulent chronic inflammation with abundant plasma cells. Previous roentgenograms revealed the following observations: The skull appeared normal. There was no evidence of active pulmonary disease. There was a moderately large

diaphragmatic hernia with partial herniation of the stomach into the retrocardiac space. There was minimal osteoporosis of the spine without destruction of bone. A calcified uterine fibroid was present. There was calcification of pelvic and peripheral vascular walls. There was reduplication of the renal pelvis bilaterally, with small bilateral renal calculi. Osteoporosis of the bones of both feet was present.

DISCUSSION

DR. ARTHUR CURTIS: This patient is a graduate nurse who was entirely normal until several years ago, at which time she noticed the development of hirsutism, striae, hypertension, atrophy of the breasts, a change in her voice, a peculiar fat pad over the shoulder area and an extensive hidradenitis suppurativa involving the axillas, breasts, perianal and vulval areas. This syndrome is known as Cushing's syndrome and may be due to pituitary basophilism or hyperplasia of the adrenal cortex. The latter may well increase the androgenic hormone secretion and produce the phenomenon seen here. Surgical excision of the axillary apocrine-bearing tissue was performed with good results. In addition the patient had deep roentgen therapy of the pituitary body. The entire hidradenitis suppurativa has subsided.

Torulosis.

M. C., a 52 year old white man, during the first week in October 1948 noticed the development of a hacking cough productive of a frothy yellowish green sputum which was occasionally tinged with blood. The cough was accompanied with severe pain in the chest. A roentgenogram made late in October revealed a "tumor" in the right lung. A series of injections of penicillin was given and caused subsidence of the cough, but the tumor persisted. The patient was admitted to the University Hospital on Nov. 16, 1948. He was well nourished and did not appear ill. Temperature, pulse and respiration were normal. There were two acneform lesions on the forehead, one on the side of the nose and two on the occipital area of the scalp. There was also a small, pea-sized granulomatous lesion with central ulceration on the upper lip. There were several small, firm, shotty lymph nodes in the left preauricular region. There was also a 2 by 3 cm. firm, freely movable lymph node in the right supraclavicular region. There were dulness, decreased breath sounds and tactile fremitus in the right upper portion of the chest posteriorly. The liver was palpable at the right costal margin on deep inspiration. The edge was smooth and slightly tender.

The results of routine examinations of the blood and urine were normal. Bronchoscopy was done, and a Papanicolaou stain on the exudate obtained revealed no malignant cells. A roentgenogram of the chest revealed a homogeneous and patchy increased density in the upper lobe of the right lung, also involving the superior segment of the lower lobe of the right lung. Microscopic examination of the supraclavicular node which was removed revealed a hyperplastic lymph node containing numerous giant cells and granulomatous areas with liquefaction. In the granulation tissue and in the giant cells were numerous yeastlike organisms with a thick capsule characteristic of Cryptococcus neoformans. Direct examination of pus from an acneform lesion on the forehead revealed numerous organisms. Microscopic examination of an acneform lesion which was removed revealed granulation tissue containing numerous cryptococci. Cultures of pus from an acneform lesion, granulomatous lesion and sputum grown on Sabouraud's glucose agar grew typical, moist, cream-colored colonies of C. neoformans. Examination of the spinal fluid revealed a pressure of 160 mm. of water. There was no block; the color was clear,

and there were 3 lymphocytes per cubic millimeter. The reactions to Kahn and Kolmer tests of the spinal fluid were negative. The total protein was 33 mg. per hundred cubic centimeters. The colloidal gold curve was perfectly flat, and the reaction for globulin was 1 +. No organism could be demonstrated either by direct examination or by culture. The spinal fluid sugar was 79 mg. per hundred cubic centimeters. Urine, stool and blood cultures all grew no organisms. The Kahn reaction of the blood was negative.

On Dec. 1, 1948, the patient was started on treatment with 6 Gm. of sulfadiazine daily. Shortly afterward a new granulomatous lesion developed behind the right ear. However, by December 23 improvement was noted in the skin lesions. The patient has been continued on treatment with 6 Gm. of sulfadiazine daily until the present time, at which time the skin is almost entirely cleared, there is some decrease in the area of increased density in the right upper portion of the chest and the spinal fluid still reveals no abnormalities. Biopsy specimens and cultures are available.

DISCUSSION

DR. EDWARD CAWLEY: This case of cutaneous and pulmonary torulosis is one of 8 cases encountered at the University of Michigan Hospital in the last fifteen years. Four of the 8 were discovered at autopsy. The present case is of interest in that, despite the presence of cutaneous lesions and pulmonary involvement for several months, the spinal fluid continues to be normal. There have been approximately 120 cases of torulosis reported in the literature to date, and in 13 of these there have been cutaneous lesions. We have encountered 3 of the 13 in this hospital. The frequent coexistence of torulosis and lymphoblastoma is worthy of further study.

Blastomycosis Cutis; Diabetes Mellitus.

N. H., a 52 year old Negro, was in good health until October 1947, at which time he acquired a nodule on the right eyebrow. There was no history of trauma. This lesion became crusted and spread rather rapidly to involve large areas on the face and right shoulder. Superficial roentgen ray therapy resulted in some involution of the lesions. In July and August 1947 the patient was placed on treatment with potassium iodide after a diagnosis of blastomycosis cutis was made at the City of Detroit Receiving Hospital. In November 1947 the lesions became worse in spite of iodide therapy. The patient had a history of diabetes mellitus. On his first admission, Oct. 1, 1948, there was a 4 by 3 inch (10 by 8 cm.) crusted lesion on the right shoulder, with minute pustules and atrophic scarring in the center. There were similar lesions on the face about the eyes, temples and on the forehead. There was bilateral ectropion. The liver was enlarged 3 to 4 cm. below the right costal margin. The remainder of the results of physical examination were normal.

The red blood cell count, white blood cell count and amount of hemoglobin were normal. Urinalysis showed a 4 + reaction for sugar. The fasting blood sugar on admission was 239 mg. per hundred cubic centimeters. Blastomycetes were demonstrated on smears made from lesions and in biopsy specimens. The Kahn reaction of the blood was negative. Roentgenograms of the chest showed no involvement.

Systemic Blastomycosis.

R. W., a white man aged 31, in November 1948 acquired a boil on the medial aspect of the left thigh, which has continued to drain. On December 24 he had

dull pain, swelling and red discoloration about the right ankle and heel. On Jan. 7, 1949, he began treatment with penicillin, and on January 15 the lesion on the right ankle was incised and the purulent contents drained. Tenderness, swelling, fluctuation and increased warmth of the lateral aspect of the right ankle were noted on admission to the Bone and Joint Service on January 21. Purulent material drained through the incision site on the lateral aspect. On the medial aspect of the left thigh was a granulomatous lesion covered with a slight amount of purulent drainage.

The total white cell count dropped from 22,500 (86 per cent polymorphonuclear cells) on January 21 to 9,900 (76 per cent polymorphonuclear cells) on March 4, 1949. Results of urinalysis, a roentgenogram of the chest and the Kahn test of the blood all showed normal conditions. Roentgenograms taken immediately after the patient's admission on January 21 revealed osteoporosis of the distal end of the right tibia and fibula with involvement of the subastragalar joint and the os calcis. The bone was curetted and a cast applied. Penicillin and sulfadiazine failed to relieve pain and a low grade fever. On February 1 the patient acquired a reddened, indurated papule on the dorsum of the left foot. On February 14 blastomycetes were found in the tissue scrapings from the ankle and the patient was transferred to the dermatology service. Organisms were also seen and cultured from the multiple abscesses of the chin lesion and from the ankle. The patient was treated with 5 cc. of 50 per cent potassium iodide solution given four times daily which was raised to 8 cc. four times daily and was finally reduced to 4 cc. four times daily on February 24 because of nausea and vomiting. The patient is now maintained on 5 cc. four times daily. On March 12 he acquired an acneform eruption of the face, back, neck and extensor surfaces of the forearms and legs. These lesions failed to reveal organisms. The thigh, chin and ankle lesions have been treated with compresses soaked with strong iodine solution and by two exposures of 100 r of filtered roentgen rays.

DISCUSSION OF PRECEDING TWO CASES

DR. CHARLES J. COURVILLE: I saw patient N. H. at the City of Detroit Receiving Hospital two years ago, when he presented a very bizarre appearance because of the lesions of blastomycosis about the eyes. He responded nicely to iodide therapy at that time. Patient R. W. presents what appears to be a widespread iododerma which complicates therapy for blastomycosis. Has a program of desensitization to blastomycin been tried or contemplated?

DR. EDWARD CAWLEY: R. W. first had a bony lesion of the right foot. At the time of operation on this foot, several specimens of bone were obtained and when studied microscopically showed the presence of large numbers of blastomycetes. As you can see, this patient also acquired cutaneous lesions of blastomycosis on the left thigh and on the chin. He has been treated intensively with iodides, and his condition has improved greatly. The organisms can no longer be found in the cutaneous lesion, but there are still some present in the foot, and amputation of the foot and leg is being considered to eliminate this focus.

DR. EUGENE HAND: While I was in training my associates and I observed a case of extensive dermatitis herpetiformis in which blastomycosis developed. When the patient was given iodine by mouth for the blastomycosis the dermatitis herpetiformis was decidedly exaggerated, and when the iodine therapy was stopped the blastomycosis would get worse.

DR. UDO WILE: Local cauterization effects cure in many cases. It is important to remove most of the diseased tissue.

Dermatitis Herpetiformis.

R. B., a white man aged 67, was admitted to the hospital on Sept. 3, 1948, complaining of sores and blisters over the entire body. They appeared first in September 1947 as pruritic erythematous papules on the ankles. Within a few hours they would increase in size to become variable-sized bullae, match head size to 4 by 5 cm. Their evolution was preceded by a burning sensation. The areas involved were limited to the legs and intercrural areas until May and June 1948, when they also appeared on the arms, neck and trunk. Essential observations were limited to the skin. The lesions were scattered over the whole integument in multiform character. The bullae ranged from 3 mm. to 2 to 3 cm. in diameter, were predominantly circular, discrete and slightly inflammatory. They contained clear amber fluid, and many were flaccid. Maculopapular lesions, crusting and scarring were present also. There was no involvement of the mucous membrane, though the scalp was involved.

Blood chemistry on admission was normal except for a leukocyte count of 12,320 white blood cells with a 4 per cent eosinophil count. Abnormality was found in urea clearance (226.1 per cent at one hour) and serum calcium and protein levels, which were moderately low. Repeated examinations revealed continued slightly decreased serum calcium levels, ranging from 8.3 to 8.8 mg. per hundred cubic centimeters. Later in his hospital course the patient displayed albuminuria, a leukocyte count of 28,000 and an eosinophil count of 22 per cent. During an episode of gross hematuria, the hemoglobin dropped to as low as 6.9 Gm. with 2,500,000 red blood cells. A biopsy specimen taken from the skin on Jan. 25, 1949, was reported as showing a classic example of dermatitis herpetiformis.

On admission, the patient had a spiking fever, with elevations of temperature to 102 to 103 F. daily, and he acquired ten to twenty new bullae daily. His course was downhill for several weeks, with the following complications: (1) thrombophlebitis of the left femoral vein, (2) generalized weakness to the point of fainting on sitting up, and (3) development, at intervals, of subcutaneous hematomas and finally gross bleeding from both kidneys, proved by retrograde pyelography. Numerous transfusions were necessary. Bullae continued to appear in "crops" involving all body areas except the mucous membranes. In January 1949 the patient stopped bleeding from his kidneys, though hematomas continued to appear beneath the skin involving areas as large as the palm of the hand. On January 25 treatment with the sodium salt of paraaminobenzoic acid was begun by mouth, 16 Gm. the first twenty-four hours and then 24 Gm. each twenty-four hours thereafter. There was immediate improvement in the condition of the skin, though on February 4 the patient had a severe sore throat, the pain being localized below the larynx. Roentgenologic studies revealed extensive abnormality of the upper part of the esophagus which was concluded to be due either to bullous formation or to hematoma. This difficulty "cleared," however, within one week, and the patient's course since has been one of dramatic improvement.

Dermatitis Herpetiformis; Diabetes Mellitus.

W. L., a white man aged 56, in mid November 1948 first noticed itching and burning of the skin on the left side of the back of the neck and along the left shoulder. Associated with this was malaise and lethargy. A week later, he began to acquire red blotches and papules over the left shoulder. His physician prescribed local application of heat and diphenhydramine (benadryl®), without effect. The lesions spread to involve the back, thighs, arms and legs. The patient had been taking a sulfonamide for the two weeks prior to admission. Past history revealed evidence of contact dermatitis to brass, hay fever and asthma and some

evidence of emotional instability. The patient was a middle-aged white man in a state of fairly good hydration and nutrition except for evidence of chronic weight loss. The temperature was 98.6 F.; the pulse rate was 78, and the blood pressure was 116 systolic and 68 diastolic. There was symmetric involvement of the skin of the trunk, arms and legs. The legs, in particular, revealed numerous vesicles and bullae with yellow fluid content. There were fewer of these bullae elsewhere. Much of the eruption on the trunk was confluent and made up of erythema and maculopapules with a tendency to vesiculation. There were no lesions of the mouth, of the face and scalp or on the palms and soles. Pitting edema of the ankles was noted; otherwise, the remainder of the examination revealed no abnormalities.

Blood hemoglobin was 16.5 Gm.; the red blood cell count was 5,100,000, and the white blood cell count, 7,600, with 50 per cent polymorphonuclear cells and 21 per cent eosinophils. An otologic consultation resulted in diagnosis of chronic tonsillitis and the observation of a hemorrhagic bleb of the right submaxillary papilla. Differential diagnoses were made of dermatitis herpetiformis, erythema multiforme bullosum, contact dermatitis, lymphoblastoma and herpes zoster.

The patient was placed on treatment with diphenhydramine, 200 mg. daily, soaks of aluminum acetate solution, 1:20, and calamine liniment applied locally. Colloidal baths, soaks of silver nitrate solution and of potassium permanganate solution and application of 5 per cent chlorophyll in a washable base were used in turn as the eruption persisted. Administration of paraaminobenzoic acid was started on the second day. The patient showed no definite improvement during the early part of the treatment. New bullae and papules appeared as the old lesions disappeared. The course was marked by remissions with flare-ups, chiefly involving the lower extremities. On March 1, 1949, the first real improvement was apparent, and sulfonamide therapy was started in an attempt to obtain better therapeutic response. A flare-up resulted in discontinuance of treatment with the drug two days later. Since then, the condition in general has improved although new lesions have reappeared steadily on the trunk and legs and also the scalp.

The following reports were made on biopsy: Jan. 13, 1949, histologic features of the skin of the left shoulder "compatible with lymphoblastoma"; January 31, picture of the skin of the right upper arm "compatible with dermatitis herpetiformis," and February 25, picture of the skin of the abdomen "compatible with pemphigus or dermatitis herpetiformis, but lymphoblastoma cannot be ruled out."

DISCUSSION OF PRECEDING TWO CASES

DR. ARTHUR CURTIS: In neither of these cases was the patient treated with sulfapyridine except for a short time in the second one. We have been using paraaminobenzoic acid in the treatment of dermatitis herpetiformis. Its chemical formula is somewhat similar to that of the sulfonamides. It is often tolerated better, and results with it have been very much worth while. The potassium salt is used in preference to the sodium salt because the large dose required may give the patient enough sodium to produce edema. We usually use 2 to 3 Gm. of the potassium salt dissolved in tomato juice and taken at intervals of three hours. A dose of 15 to 18 Gm. in twenty-four hours is adequate.

DR. UDO WILE: Borderline cases of pemphigus, dermatitis herpetiformis and erythema bullosum are at times very confusing. The criteria of itching, eosinophilia, Nikolsky sign and oral lesions may occur in all. Pemphigus erythematosus might also be considered in the differential diagnosis. Histologic changes also are not reliable, nor is the iodine test. Either pemphigus is becoming milder or more serious cases of dermatitis herpetiformis are being seen.

DR. ARTHUR CURTIS: Some sections showed suggestive evidence of lymphoblastoma in the second case.

DR. HERMANN PINKUS: The section presented from the second case looked like dermatitis herpetiformis.

Lymphoblastoma Cutis; Arteriosclerotic Heart Disease.

B. L., a white man aged 72, first had trouble with his skin three years ago when he acquired round, pruritic, erythematous, scaly lesions on his lower legs which frequently broke down and wept. He received different kinds of local therapy including an unknown amount of roentgen irradiation. This eruption cleared in about six weeks. Nine months ago a scaling, pruritic, erythematous eruption recurred which was resistant to therapy. The patient entered the hospital Jan. 14, 1949. Physical examination revealed the skin to be dry. There was pronounced lichenification over the elbows and the ulnar side of the arms and wrists. There were dry, scaling circumscribed lesions over the perineal region, thighs and both legs. There was edema and an eczematoid, weeping eruption with crusting, scaling and fissuring on both lower legs. The voice was husky. The heart was borderline in size, and the pulse irregular, with a rate of 72. The blood pressure was 140 systolic and 80 diastolic. Both testes had been surgically removed. There was no lymphadenopathy and no enlargement of the liver or spleen.

The results of urinalysis revealed no abnormalities. The Kahn reaction of the blood was negative. The blood picture was normal except for an eosinophil count of 13 per cent. The electrocardiogram was normal. The fasting blood sugar was 79 mg. per hundred cubic centimeters. A roentgenogram of the chest revealed no abnormalities. Biopsy of the skin showed the picture of lymphoblastoma cutis.

Wet dressings of 1:16 aluminum acetate solution, calamine liniment and 1 per cent salicylic acid in petrolatum were used for local therapy without improvement. Treatment with the potassium salt of paraaminobenzoic acid was started February 8, 3 Gm. every three hours during the daytime only. There was gradual drying and clearing of the skin eruption. The patient was discharged from the hospital February 14, with instructions to continue taking the potassium paraaminobenzoate 3 Gm. five times daily, to wear elastic bandages on the legs and to apply a bland ointment to previously involved skin areas.

Lymphoblastoma Cutis.

C. A. C., a white man aged 63, was generally well until January 1947, when he acquired a scaly, pruritic, erythematous patch about the size of a silver dollar in each antecubital space. The lesions cleared up with superficial roentgen ray therapy but recurred shortly afterward, and in spite of treatment the eruption became generalized. Pruritus was intense. Edema of the lower extremities developed. Along with the generalized erythroderma there was branny and flaky scaling, and most of the scalp hair and all the body hair was rubbed off. Baths, local applications of ointment and lotions and superficial roentgen ray therapy over a period of one year were of no benefit. The patient was admitted to the University Hospital on Jan. 21, 1948. He presented a universal scaly erythroderma with pronounced thinning of the scalp hair, moderate edema of the legs and feet, loss of pubic and axillary and body hair, decided dyskeratosis of the nails, a generalized discrete lymphadenopathy and a slightly enlarged liver and spleen. The skin was lichenified, infiltrated, excoriated and of a dusky red hue. The blood pressure was 120 systolic and 70 diastolic. His weight was 142 pounds (64 Kg.). The examination otherwise revealed no abnormalities.

Hemoglobin was 10 to 12 Gm. per hundred cubic centimeters. The red blood cell count was 3,800,000 to 4,700,000. The white blood cell count was 7,000 to 18,000 with an eosinophil count between 4 and 17 per cent and differential counts within normal limits otherwise. The reaction to the Kahn test was negative. Biopsies of skin showed a lymphocytic infiltrate in the dermis. Biopsy of a lymph node showed chronic hyperplastic lymphadenitis with follicular architecture preserved. A roentgenogram of the chest showed normal conditions.

Baths, wet dressings, local applications of ointments and lotions and use of antihistaminic drugs gave symptomatic relief, but no improvement was noted in the dermatosis. Three weeks after hospitalization the patient was started on treatment with sodium paraaminobenzoate, 2 Gm. every two hours, day and night. Within a few days there was noticeable improvement, with thinning of the skin and fading of the dusky discoloration, first of the face and then of the trunk. The patient was discharged from the hospital after seventeen days and continued treatment with the sodium paraaminobenzoate every two hours, coal tar solution baths daily, wet dressings of 1:16 aluminum acetate solution to all weeping areas and a keratolytic ointment to the dry scalp areas, given at home. Improvement was slow and steady. Edema of the lower extremities with fissuring of the feet persisted for several weeks, but the rest of the skin cleared and became free of scale. There was regrowth of pubic, axillary and body hair, and the scalp hair, which had always been blond, showed a luxuriant regrowth of dark-colored hair. The dosage was changed to 2 Gm. every three hours for five doses daily, and a mixture of 75 per cent potassium paraaminobenzoate and 25 per cent sodium paraaminobenzoate was substituted for the sodium paraaminobenzoate. There was a gain in weight up to 165 pounds (75 Kg.) and complete clearing of the scalp and skin, and a regrowth of normal nails by August 1948. The dose of the paraaminobenzoic acid salt was gradually reduced, and in October there were a number of infiltrated, elevated, scaly, erythematous plaques varying from 5 to 20 mm. in diameter, over the shoulders, back and arms. Biopsy showed a heavy lymphocytic infiltrate in the papillary and subpapillary portion of the dermis. The lesions subsided completely on five doses of a paraaminobenzoic acid salt given daily within four weeks. In December administration of the drug was discontinued, and in January the patient had a recurrence of scaly erythematous lesions. In February there were fifty to sixty plaques varying from 5 to 10 mm. in diameter over the back, shoulders and arms. Biopsy again showed a lymphocytic infiltrate in the dermis. Treatment with a paraaminobenzoate was again started, and the lesions disappeared completely in four weeks.

DISCUSSION OF CASES OF LYMPHOBLASTOMA CUTIS

DR. HARTHER KEIM: I saw B. L. about ten years ago with a dermatitis which, at that time, was confined to the lower legs. It was eczematoid in character, and I felt it was on a nutritional basis. He returned several times with exacerbations which responded to treatment. I have not seen him for the last seven years. Certainly the lesions on the posterior surface of the thigh clinically suggest lymphoblastoma at this time. C. A. C. has responded dramatically to paraaminobenzoates. I think it is also interesting to note that the pigment has returned in the hair shafts with regrowth.

DR. KENNETH MOORE: C. A. C. had a terrible exfoliative dermatitis with loss of hair and nails. He looks now thirty years younger than before.

DR. ARTHUR CURTIS: Remissions with sodium or potassium paraaminobenzoate in lymphoblastoma seem longer to us than those which are obtained with nitrogen mustard. The treatment, however, is only palliative and not equally

good in all patients. A recurrence of darker hair or a return to normally colored hair is seen in some cases. This phenomenon has been described in the treatment of animals who have been on diets devoid of a paraaminobenzoate when the compound is again given. There are many instances of intolerance to the drugs, and we have observed three deaths. In each there was extensive damage to the liver. Patients who manifest cutaneous sensitivity can be desensitized by starting treatment with very small doses, such as 1 grain (60 mg.), and slowly increasing the dose from that point. Fever, enlargement of the liver, nausea and vomiting and a drop in the leukocyte count are all danger signals. We have never seen a patient with frank agranulocytosis from this drug. Moderate fall in the leukocyte count, however, is not uncommon but may not be persistent. The drug is effective in some cases but not all. Like nitrogen mustard, it seems to have greater effect in mycosis fungoides and Hodgkin's disease than in other types of lymphoblastoma.

DR. UDO WILE: I have seen a most dramatic response in lupus erythematosus disseminatus after administration of the potassium salt after administration of the sodium salt had had no effect.

DR. FRANK STILES: Just for the record I want to mention that a paraaminobenzoic acid preparation was effective in treatment of warts in 1 case of my experience.

Scleroderma; Xanthomatous Infiltration of the Eyelids; Gynecomastia; Epididymitis.

D. K., a white man aged 43, in 1945 acquired erythema, swelling and pain of the legs associated with fever and a weight loss of over 20 pounds (9 Kg.) in the ensuing months. In March 1946 he had acute epididymitis on the right which within a week's time fairly well subsided with drainage and penicillin. The leg condition became more disabling, and numerous diagnoses were made by the various services by which the patient was examined. Among these were stasis dermatitis, erysipelas, thrombophlebitis, disseminated vascular disease and also lymphoblastoma because of the hepatomegaly, lymphadenopathy and suggestive picture of the biopsy specimens of the nodes. Abdominal roentgen ray treatment was given for a possible lymphoblastoma. Blood transfusions were given for hypochromic anemia. When the patient was seen early in 1947 the skin changes were clinically suggestive of scleroderma. Gynecomastia and xanthomatous lesions of the lower lids were noted, and the Aschheim-Zondek test of the urine gave positive reactions. On Feb. 16, 1948, the patient was seen to be chronically ill and almost bedridden. The skin of the left hand and the lower portions of the legs and the ankles was dark reddish brown. Atrophy was present, and the skin could not be picked up between the fingers. The toe nails and finger nails of the left hand were dystrophic. Ankle joints and joints of the left upper extremity were limited in their motion. Numerous firm nodular subcutaneous lesions were present on the medial aspect of the thighs. The breasts and epididymides were enlarged bilaterally. Xanthomatous lesions of the lower lids and bridge of the nose were present. Axillary and inguinal lymphadenopathy was noted.

The results of urinalysis were normal. The hemoglobin varied from 10 to 11 Gm. on numerous occasions but approached normal with the aid of transfusions. The usual reducing substances were found in the urine after paraaminobenzoic acid was administered. Roentgenologic studies of the hands and wrists showed osteoporosis compatible with bone changes seen in scleroderma. The patient received several whole blood transfusions and physical therapy. On February 25 the patient began treatment with sodium paraaminobenzoate and had considerable improvement

by the time of his discharge in April 1948. He was discharged on treatment with 30 cc. of a 10 per cent solution given every three hours. Follow-up examination in the outpatient clinic revealed steady improvement. When last seen, on Feb. 8, 1949, the patient had improved mobility of the joints, and the skin of the left hand was particularly improved, being warm, moist and pliable. He had gained 40 pounds (18 Kg.) since the start of medication.

Scleroderma.

A. E., a white woman aged 23, had the beginning of her illness in July 1947 as facial swelling and a macular rash about the face and neck. Soon the hands, wrists, feet and ankles became swollen and painful on motion, and movement became limited. For about one year there was progressive involvement of the aforementioned joints and surrounding tissues, and, in addition, the knees, elbows and shoulders had limitation of motion, stiffness and pain on movement. For the past six months the functional state of the joints has remained stationary. The skin of the face and hands has become thinner and more flexible. The skin of the face, neck, hands, arms, feet and legs is indurated, shiny and discolored and can be picked up between the fingers only with considerable difficulty. The face and hands show greatest involvement. Full range of motion is lacking at the shoulder, elbow, wrist, fingers, knee, ankle and temporomandibular joints. The spleen is palpable 2 fingerbreadths below the costal margin, and the liver descends 3 fingerbreadths on inspiration. There is a deformity of the lip, the residual of a previous harelip repair. The thyroid was enlarged diffusely.

A mild hypochromic anemia has been consistently present. The white cell count has been normal except during times of sensitivity to paraaminobenzoates, when the total count has dropped to 3,400 with 43 per cent polymorphonuclear cells and 55 per cent lymphocytes. The urine has been normal except for the presence of reducing substances while the patient was on paraaminobenzoate therapy. The creatine in the urine was 2.94 Gm. per twenty-four hour output. The blood sedimentation rate has been moderately elevated. Roentgenograms of bones revealed generalized osteoporosis. Biopsies of skin and muscle in July 1948 were not diagnostic of scleroderma. Under treatment with acetylsalicylic acid and physical therapy the patient showed little objective and minimal symptomatic improvement. Upon two occasions when a paraaminobenzoate was administered in the usual doses, the patient had fever, nausea and vomiting and neutropenia so that a trial of tetraethylammonium chloride was initiated. Under this treatment the patient claimed some relief of symptoms, although again no definite objective evidence of improvement was present. The patient was subsequently hospitalized and desensitized to paraaminobenzoates by oral administration, beginning with minute doses and then gradually increasing them until it became possible for the patient to take the usual maximum therapeutic doses of 18 Gm. a day. Under this treatment the edema and induration of the skin of the face and hands and feet have definitely decreased. There has been no change, however, in joint motion or in functional ability in that the activity of the patient is as much restricted as previously.

DISCUSSION OF CASES OF SCLERODERMA

DR. ARTHUR CURTIS: D. K. was presented to show the effect of paraaminobenzoate treatment of scleroderma. His improvement has been remarkable, since he was an invalid when he came in and now is a self-sustaining person. He has not been given the drug since January.

DR. FRANK STILES: We have heard the discussion of four different diseases which appear to be unrelated, all of which have been treated with paraaminobenzoic acid preparations. It would be interesting to hear a discussion of the rationale.

DR. ARTHUR CURTIS: Paraaminobenzoic acid was first used in the treatment of African scrub typhus infection. Dr. Rothman showed its value in the absorption of ultraviolet radiation and as a skin protective agent. These observations led to our using it in lupus erythematosus, and later the other collagenous tissue diseases. Its chemical formula is like that of urethane, which has been shown to have value in the treatment of the lymphoblastomas, particularly the leukemias. It is for that reason we used it in this group.

Lupus Erythematosus, Discoid Type, of the Face. Miliary Tuberculosis (Quiescent).

DISCUSSION

DR. ARTHUR CURTIS: This patient was presented because he has both discoid lupus erythematosus and proved tuberculosis. The occurrence suggests the possibility of a relation between the two diseases, or it may be purely accidental. The interesting thing is that on two occasions the use of streptomycin for the treatment of the tuberculosis has also improved the lupus erythematosus.

Boeck's Sarcoid.

E. V., a white woman aged 54, acquired itching "mosquito bite" lesions on the left arm nine years ago. Gradually each lesion extended at the periphery and new lesions of similar nature appeared on the right arm, the back and the knees. None of the lesions involuted. The lesions consist of brownish purple infiltrated plaques of varying sizes from that of a small coin to almost palm size on the extensor surfaces of the arms near the elbows, on the knees and on the lower part of the back and upper portion of the buttocks. The liver descends 3 fingerbreadths on inspiration.

A roentgenogram of the chest reveals bilateral hilar lymphadenopathy. There is a suggestion of cystic lesions in the phalangeal bones of one finger. The blood count and results of urinalysis were normal. Total serum proteins were 7.1 Gm., with albumin, 4.7 Gm. and globulin, 2.4 Gm., per hundred cubic centimeters, with an aluminum-globulin ratio of 2.0. The Kahn test of the blood gave a negative reaction. Biopsy of the large lesion of the left arm revealed noncaseating epithelioid tubercles in the dermis.

DISCUSSION

DR. HERMANN PINKUS: The histologic picture is typical of Boeck's sarcoid.

DR. ARTHUR CURTIS: Recently we have been using vitamin D_3 in doses of 50,000 units three times a day in the treatment of sarcoidosis. It is likewise tolerated poorly in some cases, as is dihydrotachysterol and calciferol. This intolerance to vitamin D preparations in sarcoidosis in contrast to the tolerance to them in lupus vulgaris has been an enigma to me. We have not yet studied vitamin D_3 long enough to know whether it is any more valuable than vitamin D_2 or dihydrotachysterol.

Marginal Glossitis (Moeller's). Presented by DR. GEORGE B. SEXTON, London, Ontario, Canada.

Mrs. B. McF., a white woman, aged 60, had an eruption in the mouth which commenced in January 1948. Various forms of medication were utilized, including

vitamin A and the B complex, ascorbic acid, penicillin, liver, various mouth washes and caustic applications. There have been intervals of quiescence and at times mild inflammation only and at other times erosive lesions. These have involved the margin of the tongue, the buccal area and the region along the line of the gums. The patient has been otherwise in good health.

Present examination reveals decidedly inflamed, erosive, tender lesions on either side of the tongue and along the margin of the gums. The blood picture was as follows: hemoglobin, 84 per cent; red blood cell count, 3,920,000, and white blood cell count, 4,450. The blood Wassermann reaction was negative. Blood sugar was not elevated. A biopsy specimen revealed a vascular connective tissue hyperplasia quite densely infiltrated with lymphocytes, plasma cells, eosinophils and neutrophils. There was no epithelial covering on the surface and no evidence of tumor growth either of a benign or of a malignant nature.

DISCUSSION

DR. EUGENE A. HAND: It is my opinion that the glossitis and stomatitis are due to phenolphthalein in the cathartics the patient admits taking over a long period. Phenolphthalein lesions in the mouth often are painful. They often are associated with genital lesions also, particularly in males.

DR. UDO WILE: The lesions looked like pemphigus, but the patient had anesthesia of the cornea and pharynx, and the lesions may be factitious.

DR. GEORGE B. SEXTON: The patient when first observed presented areas in the buccal mucosa suggestive of leukoplakia, as well as the erosive inflammatory lesions seen on the marginal aspects of the gums. Vitamin A, 750,000 units daily, was administered, with complete resolution of the mucosal plaques. The possibility of artefact was considered, but so far no admission of interference has been obtained nor does there appear to be anything elicited in the history in this woman's background to suggest the diagnosis. It was of particular interest to me to hear that phenolphthalein lesions of the mouth may be painful. The patient has been ingesting a laxative containing this drug since January 1948 but not prior to the onset of the eruption. I could classify the condition only as a marginal glossitis of a possible neurogenous origin.

Lichen Sclerosus et Atrophicus. Lichen Planus Atrophicus? Presented by DR. A. C. CURTIS and the Staff of the Department of Dermatology, University Hospital, Ann Arbor, Mich.

Kaposi's Idiopathic Hemorrhagic Sarcoma. Presented by DR. A. C. CURTIS and the Staff of the Department of Dermatology, University Hospital, Ann Arbor, Mich.

Scrofuloderma. Presented by DR. A. C. CURTIS.

Boeck's Sarcoid and Old Syphilis. Presented by DR. A. C. CURTIS.

Xanthoma, Secondary to Lipemia: Re-Presentation of a Previously Shown Case. Presented by DR. EUGENE A. HAND.

NEW YORK DERMATOLOGICAL SOCIETY

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Jan. 25, 1949

A Case for Diagnosis (Lichen Spinulosus?). Presented by DR. GEORGE M. LEWIS.

B. L., a woman aged 23, first became aware of her skin disorder two years ago while in Florida. A depigmented area, rather scaly and devoid of hair, appeared on one arm. Other scaly, slightly raised, erythematous, asymptomatic areas then occurred on the trunk and extremities over a period of months. It

was then noticed that the erythematous, scaly areas no longer occurred but that there appeared simply depigmented patches that enlarged peripherally with concomitant hair loss. Recently the eruption has spread to the face. Dermographia has been present since childhood. For the past several years the patient has had allergic bronchitis.

She gives a history of varied treatment: the administration of vitamin A, 100,000 units daily orally for three to four months, roentgenotherapy (unknown number of exposures) and application of various unknown ointments and lotions. All these therapeutic efforts were ineffectual.

There is follicular hyperkeratosis of small oval to round areas, as well as of giant-sized areas. These areas are devoid of hair and apparently are deficient in pigment.

Biopsy showed the vessels of the midcutis and upper portion of the cutis to be dilated and their walls thickened. About these was a moderate focal and cellular infiltration. Some interstitial edema was present in the upper part of the cutis. The epidermis was regularly acanthotic, and the palisade layer was intact. There was no edema of the epidermis, but on the surface was an occasional small vesicle. The follicles were dilated, and about them was a moderate cellular reaction. In one of the follicles there was a peculiar degenerative material. The cellular reaction was composed of small round cells, wandering connective tissue cells and an occasional polymorphonuclear cell.

Dr. Wilbert Sachs's microscopic diagnosis was as follows: "The process was that of a neurodermatitis reaction, and if the follicular reaction was unrelated to the rest of the process, two diagnoses would have to be entertained: one of neurodermatitis or possibly nummular eczema with a follicular process not unlike that seen in avitaminosis or pityriasis rubra pilaris. However, if one diagnosis is entertained, then the process would be considered dermatitis and follicular neurodermatitis."

Scrapings from the skin were repeatedly negative for Malassezia furfur and other fungi.

The hemogram showed hemoglobin, 76 per cent; red blood cells, 3,890,000, and white blood cells, 5,300, with 57 per cent polymorphonuclear leukocytes, 31 per cent lymphocytes, 9 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils.

DISCUSSION

DR. PAUL E. BECHET: A spiny hyperkeratosis is present, but a typical lichen spinulosus shows spines which are much longer and more grouped than in this case, in which there are some inflammatory and even atrophic changes in the skin itself, which are not usually present in lichen spinulosus.

DR. ANTHONY C. CIPOLLARO: I can offer no diagnosis other than the one presented.

DR. GEORGE M. LEWIS: The features that Dr. Traub mentioned, namely the apparent depigmentation and loss of hair in patches, all seemed to be at variance with the published description of lichen spinulosus. The biopsy report is also not in conformity. I thought, as Dr. Traub did, that a good deal of this apparent lightening effect might be due to the sun screening of the skin by the lesions.

A Case for Diagnosis (Pseudopelade? Folliculitis Decalvans?). Presented by DR. ANTHONY C. CIPOLLARO.

M. R., a woman aged 70, has been under my care for the treatment of basal cell epitheliomas of the nose and forehead. An incidental observation is the lesion of the scalp, for which the patient is now presented. The only history

obtainable was that a bald spot appeared on the top of the scalp at the age of 20 and gradually increased in extent.

A palm-sized area of alopecia is seen at the vertex of the scalp. The area is round, smooth, soft, white, atrophic and completely devoid of hair. It presents an "onion skin" appearance. There are several split pea–sized, adherent, superficial crusts. Posterior to this area in the upper part of the occipital region in a palm-sized area, the hair follicles manifest slight erythema. No suppuration is present. No treatment has been prescribed.

DISCUSSION

DR. GEORGE C. ANDREWS: I wonder whether biopsy of the larger patch where it is swollen and edematous wouldn't be advisable. There have been cases of lichen planus atrophicus reported in England resembling pseudopelade.

DR. GEORGE M. LEWIS: I wonder whether favus shouldn't be considered. I don't know how it can be excluded definitely. The condition might be an old, burned-out case.

Poikilodermatomyositis. Presented by DR. J. LOWRY MILLER.

A. B., a Puerto Rican woman aged 30, is presented from the Vanderbilt Clinic, where she was first seen by me on May 28, 1940, complaining of increasing stiffness of the face, hands, left arm and knee of five years' duration.

The past history was irrelevant except for four pregnancies which resulted in full term babies weighing about 3 pounds (1,361 Gm.), all of whom died before the age of 3 months. She had had no miscarriages. The patient has lived in the United States since 1927 and was in good health until the onset of the present illness in 1935. She then noticed swelling and tenderness of her arms, hands and feet accompanied with generalized muscular aching and general malaise. The swelling gradually decreased. As the months passed she noticed that the skin over her hands and arms became dry, taut and thick and had a glossy appearance. The muscles of her hands became thin, tender and painful on pressure. The slightly drawn skin limited the motion of her fingers, wrists and elbows, particularly those of the left arm. She became easily fatigued. In 1939 her eyelids and parts of her face became swollen.

The patient was admitted to the Hospital for Joint Diseases in 1939. She had lost 30 pounds (14 Kg.) during the preceding four years. The skin of the jaw was firm, smooth and shiny but not boardlike. The lids of both eyes, especially the lower lids, were puffy, bluish red and discolored. Irregular, circumscribed, reddish patches were seen on both lids. Within these areas were telangiectases, deep pigmentation and slight scaling. The patient was unable to open the jaw widely, and there were boardlike hardness and muscular atrophy of both hands and forearms. The left elbow was flexed at about 45 degrees and could not be extended. The hand showed moderate flexion deformity of the fingers, with inability to flex or to extend. The skin of the ankles, legs, knees and lower third of the thighs was of boardlike hardness. The feet were not involved. The left knee could not be flexed beyond 45 degrees. The skin over points of pressure was red and scaling. The fingers were long and thickened at the interphalangeal joints. The overlapping skin was hard, smooth and shiny, with patches of pigmentation.

Many laboratory procedures gave essentially normal results. Roentgenograms of the left maxillary sinus showed clouding. The erythrocyte sedimentation rate was 40 mm. in forty-five minutes. The blood calcium was 9.2 mg. per hundred

cubic centimeters. The urine (twenty-four hour output) showed 862 mg. of creatinine and 200 mg. of creatine.

Biopsy in 1939 (Hospital for Joint Diseases) of a section of skin showed chronic inflammation in the subepidermal layer. Fragmentation of collagen fibers in the subpapillary layer was present. The epidermis was normal except for slight alteration cavitaire. A section of muscle from the more active myositis of the thighs showed islets of lymphocytic infiltration between the muscle bundles. Hyaline degeneration of the muscle bundles was present. In one of the hyalinized muscles a blood vessel with a thickened wall was seen.

Treatment consisted of a sinusotomy of the left maxillary sinus and administration of wheat germ, 2 to 3 tablespoons (30 to 45 ml.) a day, and alpha tocopherol, 50 mg. intramuscularly over a period of a week, supplemented by the administration of vitamin A and yeast.

Aside from occasional exacerbations the patient has made steady progress, and the process is now quiescent except for residual thickening of the skin over the elbows and hands.

DISCUSSION OF PRECEDING TWO CASES

DR. A. BENSON CANNON: I should never have guessed that the first patient had dermatomyositis. The skin presents every appearance of scleroderma, with hard, shiny, pigmented areas that give the patient a masklike, almost mummified appearance. The patient is extremely thin, and I should judge the prognosis was poor.

DR. PAUL GROSS (by invitation): I have known the first patient for many years, and observed her during the active stage of her disease. She had typical edema of the eyelids and malar region, associated with cyanotic erythema. The lesions of poikiloderma were present over the elbows and knuckles and on the thighs, and she had episodes of acute myositis, especially of the upper extremities. There are calcium deposits in the shoulder girdle and also some in the skin of the fingers. As Dr. Miller said, this is a burned-out case of dermatomyositis. I could not tell what was responsible for the patient's recovery, but at the time of the activity of the disease she received treatment with pantothenic acid, alpha tocopherol and soybean lecithin. Through social service we arranged for a high caloric diet. There has been no recurrence of myositis for a long time. In conclusion, this case fits very well into the group of cases which were originally called scleroderma atrophicans, a name which was later changed to poikilodermatomyositis.

DR. GEORGE M. LEWIS: There is little evidence of poikiloderma at this time. Is it common for those lesions to disappear?

DR. FRANK E. CORMIA: I was interested to hear that Dr. Gross considers this a burned-out case. It is somewhat reminiscent of that of a patient on whom autopsy was performed at New York Hospital. There was considerable difficulty in making a diagnosis, but there was masked atrophy as shown in this case. At autopsy there was observed widespread atrophy and secondary scleroderma. I suspect, as does Dr. Cannon, that the prognosis may be poor for this person despite the apparent arrest of the active process.

DR. J. LOWRY MILLER: I thought the evidence that this was a burned-out case was fairly good. The patient is now in the ninth year since being in the hospital, when she was desperately ill. The attacks of fever have ceased. There are no signs of new lesions, and she has been well for at least five years. There are some changes of poikiloderma around the finger nails and in the skin of the elbows, but most such lesions have disappeared.

DR. GEORGE C. ANDREWS: I have seen the second patient on the ward, and she is deteriorating rapidly, growing weaker every day. On examining the skin carefully one can seen petechiae, and there seem to be some vascular changes, as there often are in these cases. She has been receiving tripelennamine (pyribenzamine®) for a long time and a high caloric diet without apparent benefit. She is now receiving alpha tocopherol and rutin.

DR. J. LOWRY MILLER: I believe, as Dr. Gross says, that if you can get these patients through the acute period they can achieve the condition of the patient first presented. On discharge from the hospital they should be given an exceptionally nutritious diet and kept as active as possible.

A Case for Diagnosis (Lichenoid Sarcoid? Leprosy?). Presented by DR. EUGENE F. TRAUB.

M. S., a woman aged 46, complained of an eruption on the hands and forearms of something over a year's duration. The patient's mother, who was born in Germany, acquired an eruption on the hands in 1920 or 1922. She was seen by Dr. Ormsby off and on until her death in 1923, and it was never settled whether or not she had leprosy. The patient was born in this country but has traveled around the world and visited the interior of China for several months on a world cruise. There was some question of tuberculosis, and she had pleurisy about a year ago, although at present there is no active tuberculosis, according to a roentgenologic examination of the chest. She recently had her tonsils removed because it was thought there might be a relation between a focus of infection and the eruption.

The eruption is limited to the hands and forearms, extending to the elbow, with a bandlike patch of lesions on the back of the right hand. It has a brownish, purplish color. When it was seen earlier, one of our members thought it might be granuloma annulare because of the annular configuration of the lesions. The eruption has spread since then and is now rather extensive on the backs of the hands and the forearms to the elbows, mostly on the extensor surfaces. There is some lichenification under artificial light, so that lichen planus was considered, but on careful inspection that diagnosis was easily excluded. I then thought of lichenoid sarcoid or leprosy. Dr. Machacek agreed with a diagnosis of lichenoid sarcoid but will do further studies with the idea of ruling out leprosy. I have written to Carville for lepromin but haven't received it yet.

The reaction to the tuberculin test was 2 to 3 + with a dilution of 1 : 1,000,000, and at 1 : 100,000 was 4 +. The Wassermann reaction was 4 +.

There is an enlarged ulnar nerve on the right side, and some sensory change in that the patient has difficulty in distinguishing sharp from dull. The temperature sense was not tested.

DISCUSSION

DR. ANTHONY C. CIPOLLARO: If the question of leprosy had not come up, my first impression would have been that of sarcoid of Boeck's superficial type. Now, in view of the fact that the pathologic picture supports that contention, I would consider the condition a Boeck type of sarcoid and treat it accordingly. I suppose the patient has had roentgenologic examinations of the chest and long bones and that examinations revealed no evidence of sarcoid there. I would certainly discount the history of the mother's possibly having had leprosy and would discount the history of a tour through central China as possibly having caused the patient to be exposed to leprosy. I would consider the condition sarcoid on the clinical and histologic evidence presented.

DR. J. LOWRY MILLER: I think the lesion is unquestionably sarcoid, but having seen a number of cases of leprosy with sarcoid-like lesions, I think further studies to prove or disprove the presence of that disease should be made.

DR. FRANK E. CORMIA: I agree with Dr. Costello that, while the lesions do resemble the lichenoid type of sarcoid, I find it difficult to reconcile the strongly positive reaction to the tuberculin test with sarcoidosis. A diagnosis of lichenoid tuberculosis should be considered. If I recall correctly, internal tuberculosis is not infrequently present, and so I suggest that a thorough search be made.

DR. PAUL GROSS (by invitation): I agree with Dr. Cormia that it is difficult to reconcile the positive reaction to the tuberculin test in this patient with the diagnosis of sarcoidosis. I remember a similar case in which Dr. Machacek established the diagnosis of tuberculosis in a patient who had a history of renal tuberculosis.

DR. A. BENSON CANNON: I am convinced that the patient has leprosy. The color of the papules, the wrinkling and shininess of the skin, the softness of the lesions and the enlarged ulnar nerve with changes in sensation are all symptoms of leprosy. I don't believe that any test other than one showing lepra bacilli would influence me in making a diagnosis. Examination of the secretion from the nose for lepra bacilli, as well as examination of the lesions themselves, should be made.

DR. PAUL E. BECHET: It is at times extremely difficult clinically to differentiate nodular leprosy of the annular type from Boeck's sarcoid or a serpiginous syphiloderm. Even histologically there may be a sarcoid type reaction in leprosy and syphilis. I have on several occasions heard both the late Drs. Pollitzer and Highman disagree on the diagnostic significance of a particular slide in the differential diagnosis of these three diseases. I believe that further microscopic study is essential for arriving at a correct diagnosis.

DR. GEORGE C. ANDREWS: There might be a positive reaction to the tuberculin test in leprosy too. The lepromin test is not diagnostic of leprosy. It is useful only in determining the prognosis and therapeutic progress of the case.

DR. JOSEPH C. AMERSBACH (by invitation): We are all in accord that a thorough study should be made to establish a true diagnosis. I should prefer to await the observations on biopsy. Only in this manner can a definite diagnosis be established.

DR. LESLIE P. BARKER (by invitation): I think this patient has a lichenoid type of sarcoid. The dusky color of some lesions in conjunction with atrophy of the right thenar eminence, however, suggests leprosy. Further microscopic studies are necessary to rule out this disease.

NOTE.—The patient was lost to observation, but indirect information was later received that administration of streptomycin caused the eruption to clear up completely.

Pityriasis Rubra Pilaris. Presented by DR. A. BENSON CANNON.

P. W., a Negro aged 10, is presented from the Vanderbilt Clinic with a generalized asymptomatic eruption of three months' duration. The patient awoke one morning with a red face. This redness soon spread, to involve his whole body within two days, and within a week his skin began to get rough and dry. This condition has persisted until now without change. At the onset of the eruption he had no symptoms to suggest an infectious exanthem. The patient

gives no history of taking medication, and his only other complaints are those of frequent micturition and enuresis.

The eruption is generalized, sparing only the middle of the face and the medial aspect of both knees, extending halfway down the legs. The primary lesion appears to be a follicular hyperkeratotic plug on an erythematous base. These plugs are particularly noticeable on the dorsal surface of the proximal phalanges of the fingers. Both palms and soles are dry, hyperkeratotic and fissured.

The boy's teeth are abnormal in that the incisors are large, wedge shaped and notched. There is a slight ectropion of his lower eyelids, and the conjunctivas seem paler than normal.

DISCUSSION

DR. PAUL E. BECHET: I could feel no stiff hair over the dorsal surface of the hands, particularly the phalanges. I agree with the diagnosis. I had one patient that did very well on treatment with thyroid extract.

DR. GEORGE C. ANDREWS: I examined the child pretty carefully yesterday and agree with Dr. Cannon that the condition is pityriasis rubra pilaris. The onset is not unusual. The clinical appearance is characteristic, with thickening of the palms and soles and horny papules over the dorsal surfaces of the phalanges. I think biopsy will settle the diagnosis.

DR. PAUL GROSS (by invitation): This type of pityriasis rubra pilaris in children frequently has a sudden onset and develops into generalized erythroderma. The response to vitamin A therapy and liver injections is very satisfactory in these cases.

Lupus Erythematosus; Neurosyphilis. Presented by DR. J. LOWRY MILLER.

N. C., a woman aged 50, states that a cluster of small "pimples" appeared on the right side of the chin, developing into pustules and leaving scars when they disappeared. A red patch developed about the same time and has persisted. The patient was given four roentgen ray treatments by a local physician a year ago, with no improvement. The area has remained about the same since.

The patient said she had a series of "cysts" on the outer surface of each ear about two and a half years ago. She said the "cysts" were quite red and that when they disappeared they left scars. She has been treated for syphilis since 1926, receiving a total of 40 bismuth preparation and 55 mercury preparation injections. In 1947 she received 7,300,000 units of penicillin in conjunction with fever therapy. In 1948 she received 6,000,000 units of penicillin. Treatment with penicillin was discontinued because of an urticarial reaction.

On the right side of the chin is an irregular-shaped erythematous, nonelevated area measuring about 2.5 by 1 inch (6 by 2.5 cm.). This is slightly elevated above the surface of the skin and is studded over with many small, deep-seated, pitted scars about 2 to 3 mm. in diameter. There are a few dilated follicular openings and several comedo-like lesions in the area. On the outer side of the ear there is considerable scarring with dilated follicles and comedo-like lesions, but no erythema.

On Oct. 7, 1947, the Kolmer reaction of the spinal fluid was 444--; on July 13, 1948, it was 44---. The cell count, colloidal gold reaction and total protein determinations were normal. The serologic tests for syphilis on the blood gave negative reactions on Oct. 17, 1947 and Dec. 20, 1948.

A biopsy specimen of the lesion on the chin was diagnosed as lupus erythematosus.

Treatment has consisted of the administration of gold and sodium thiosulfate. A total of 75 mg. has been given during the past week.

DISCUSSION

DR. ANTHONY C. CIPOLLARO: I agree with the diagnosis as presented.

DR. LESLIE P. BARKER (by invitation): I have followed this patient at the clinic for several years. The lesions of lupus erythematosus developed while she was receiving bismuth injections for the treatment of syphilis. I have seen this development occur on several occasions, and it has convinced me that bismuth has very little value in the treatment of lupus erytematosus.

DR. JOSEPH C. AMERSBACH (by invitation): I wonder how much damage to the liver has been caused by the use of arsenicals and heavy metals in the treatment of syphilis. This might be one of the factors in precipitating the lupus erythematosus. I have a patient who has been under treatment for lupus erythematosus at the Skin and Cancer Unit for years with no apparent improvement. For the past eight months to two years he has received large doses of liver extract intramuscularly three times a week, with great improvement, that is, with regression of the cutaneous lesions and disappearance of the telangiectasia which is so frequently seen in widespread disease of this kind.

DR. PAUL E. BECHET: This case represents a classic example of lupus erythematosus hypertrophicus et profundus, as reported by me some years ago (ARCH. DERMAT & SYPH. **45**:33 [Jan.] 1942). The location, cartilaginous infiltration and cribriform scarring are characteristic, and the photograph of 1 of the patients in my article shows a condition identical in appearance with that of Dr. Miller's patient. The cases reported by Irgang, Arnold and others under the designation lupus erythematosus profundus present an entirely different clinical picture from lupus erythematosus hypertrophicus et profundus and clinically suggested sarcoidosis, but in Arnold's case the histologic picture was that of lupus erythematosus.

Pemphigus. Presented by DR. GEORGE C. ANDREWS.

A Case for Diagnosis (Pemphigus?). Presented by DR. GEORGE C. ANDREWS.

Folliculitis of the Scalp; Dermatitis Papillaris Capillitil (Neck). Presented by DR. A. BENSON CANNON.

Necrobiosis Lipoidica Diabeticorum Sine Diabetes. Presented by DR. J. LOWRY MILLER.

NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

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Jan. 3, 1949

Sensitivity to Paraphenylenediamine and to Unrelated Azo Dyes. Presented by DR. SAMUEL M. PECK.

S. B., a woman aged 41, is presented from Mount Sinai Hospital. In July 1947 she acquired dermatitis over sites where stockings are worn and in the elbow flexures. Patch tests at that time were positive to paraphenylenediamine (4 +) and to her nylon hose (2 +). This attack cleared up. In May 1948 there was a recurrence of the dermatitis on the legs, dorsa of the feet and buttocks. Patch tests to new nylon hose and other materials were negative, except for a positive reaction to leather from a black shoe. The patient was admitted to the hospital in September 1948 with a generalized dermatitis which cleared up in several weeks. Results of patch tests were as follows: with paraphenylenediamine, 3 +; with methyl red, 3 +, and with methyl orange, 1 +.

DISCUSSION

DR. SAMUEL M. PECK: Dr. C. L. Mayer has informed me that the situation is not so much cross sensitivity but apparently a change in chemical structure which takes place on the skin surface. With the development of various types of cross sensitivity to apparently unrelated substances, we shall have to worry about clothing dyes again.

Dermatitis Herpetiformis. Presented by DR. SAMUEL M. PECK.

A. H., a woman aged 33, is presented from Mount Sinai Hospital with a generalized eruption of eleven years' duration. Two months before confinement the patient noticed an eruption on her chest which was suggestive of herpes zoster. This cleared up in a few weeks. A month after delivery blister-like lesions appeared on the knees and elbows, and from then on she was never free from the eruption, which was always associated with chills and fever. She went to the Medical Center, where the condition was considered allergic in origin. She has been under the care of many other physicians without benefit, and her condition failed to improve with calcium gluconate therapy. About two years ago she was under the care of Dr. Hailey of Atlanta, Ga., who prescribed sulfadiazine, which gave the best results.

There are numerous grouped papulovesicular lesions in typical locations, such as on the buttocks, genital region, scalp and ankles. Most of the lesions are excoriated, as the eruption is extremely pruritic. There is some scarring but no pigmentation.

The vesicle fluid contained 56 per cent eosinophils. A patch test with 50 per cent potassium iodide elicited positive reactions.

DISCUSSION

DR. JOEL SCHWEIG (by invitation): This morning the reactions to patch tests were still negative. Tonight papular vesicles had appeared in the area where 50 per cent potassium iodide ointment had been applied. There is a psychosomatic aspect in this case. The patient had an automobile accident one year ago in which her husband was killed but she escaped unhurt. A few weeks later she acquired the lesions seen tonight. Later on she had an eruption simulating herpes zoster which cleared up when she gave birth to a child. Two months after confinement the present eruption appeared. The condition has been greatly improved by treatment with sulfadiazine prescribed by Dr. Hailey. The only thing that makes us a little hesitant to accept the diagnosis is that after eleven years we should expect some pigmentation and more scarring.

DR. PAUL GROSS: I agree that in some cases of dermatitis herpetiformis the temporary effect of sulfapyridine is dramatic provided that one is dealing with a typical case. It is unfair to refute the diagnosis of Duhring's disease after seeing the patient only once. One might say that one of the typical features of the disease is the absence of characteristic lesions at times. Repeated inspection is necessary in many instances to establish the diagnosis.

Amyloidosis Cutis (Localized). Presented by DR. SAMUEL M. PECK.

G. L., a man aged 70, is presented from Mount Sinai Hospital with generalized intolerable itching of three months' duration and an eruption on his legs.

On the legs, and especially on the right, there are many pea-sized, conical, smooth, slightly translucent, firm papules. The surrounding skin is lichenified and pigmented.

Biopsy showed areas of surface atrophy with loss of rete pegs. The subjacent corium showed pale, eosinophilic, relatively acellular stromal masses. There dilated arterioles and venules were prominent, extending into the subcutaneous tissue. There was a mild perivascular inflammatory infiltrate with eosinophils present. Staining with methylrosaniline chloride revealed the presence of amyloid. The histologic diagnosis was amyloid infiltration of the skin.

On Oct. 19, 1948, the patient began to take 25,000 units of vitamin A three times a day, and with this treatment the lesions have greatly regressed.

DISCUSSION

DR. SAMUEL M. PECK: I should like to have some of the older dermatologists tell we whether they have seen spontaneous regression in this disease. I can't see what vitamin A has to do with amyloid metabolism.

DR. LOUIS TULIPAN: Although this is a persistent and chronic disease, in some cases of amyloidosis there is spontaneous improvement.

DR. DAVID BLOOM: I have watched cases for years and have seen no regression at all.

DR. HOWARD T. BEHRMAN: One of the features of amyloidosis cutis is the fact that it is commonly recalcitrant to all forms of treatment. These patients complain of extreme pruritus, and I. have attempted unsuccessfully to relieve several of them with fairly large doses of roentgen rays. I think it is extremely unusual that so typical a case as this should have shown such a result. We must give some credit to vitamin A, with a question as to whether some other factor might not be responsible.

DR. MABEL G. SILVERBERG: The man says the itching is reduced, but he still has typical amyloidosis on the right leg.

Papulonecrotic Tuberculids and Acnitis. Presented by DR. SAMUEL M. PECK.

A. H., a woman aged 32, entered Mount Sinai Hospital in 1944 with enlarged cervical lymph nodes. Biopsy was performed, and a diagnosis of tuberculosis was reported. Since that time she has had multiple ulcerations on both legs, and an acne-like eruption has been present on the face since November 1947.

The reaction to the tuberculin test was 4+ to a dilution of 1:100,000. The Wassermann reaction was negative, and the Kahn reaction, 3+. The patient has received treatment with bismuth preparations.

DISCUSSION

DR. LOUIS TULIPAN: The patient presents erythema induratum with the typical location and the characteristic nodules and ulcerations.

A Case for Diagnosis (Pemphigus?). Presented by DR. SAMUEL M. PECK.

J. V., a woman aged 48, was studied at Mount Sinia Hospital from January to April 1948 because of alopecia areata, dermatitis of the face and ears and a vesicular eruption of the mucous membranes. The cutaneous eruption was of five years' duration and has cleared up under treatment. The mucous membrane lesions are of one year's duration and persist.

Impressions during her previous admission were as follows: 1. Contact dermatitis in which sensitization played a minor role was present. 2. The causative factor reached the skin through the blood stream. 3. The oral lesions and flare following the use of antiseptics pointed either to an infection (virus or bacterial) or to an allergy of obscure type (food?). 4. A psychosomatic component was present but did not predominate.

While in the hospital the patient failed to respond to various forms of local therapy or to elimination diets. The administration of penicillin had no effect. Local application of iodochlorohydroxyquinoline (vioform®) ointment, 3 per cent, helped the cutaneous eruption. The superficial ulcers of the tongue and gums failed to respond to any therapy.

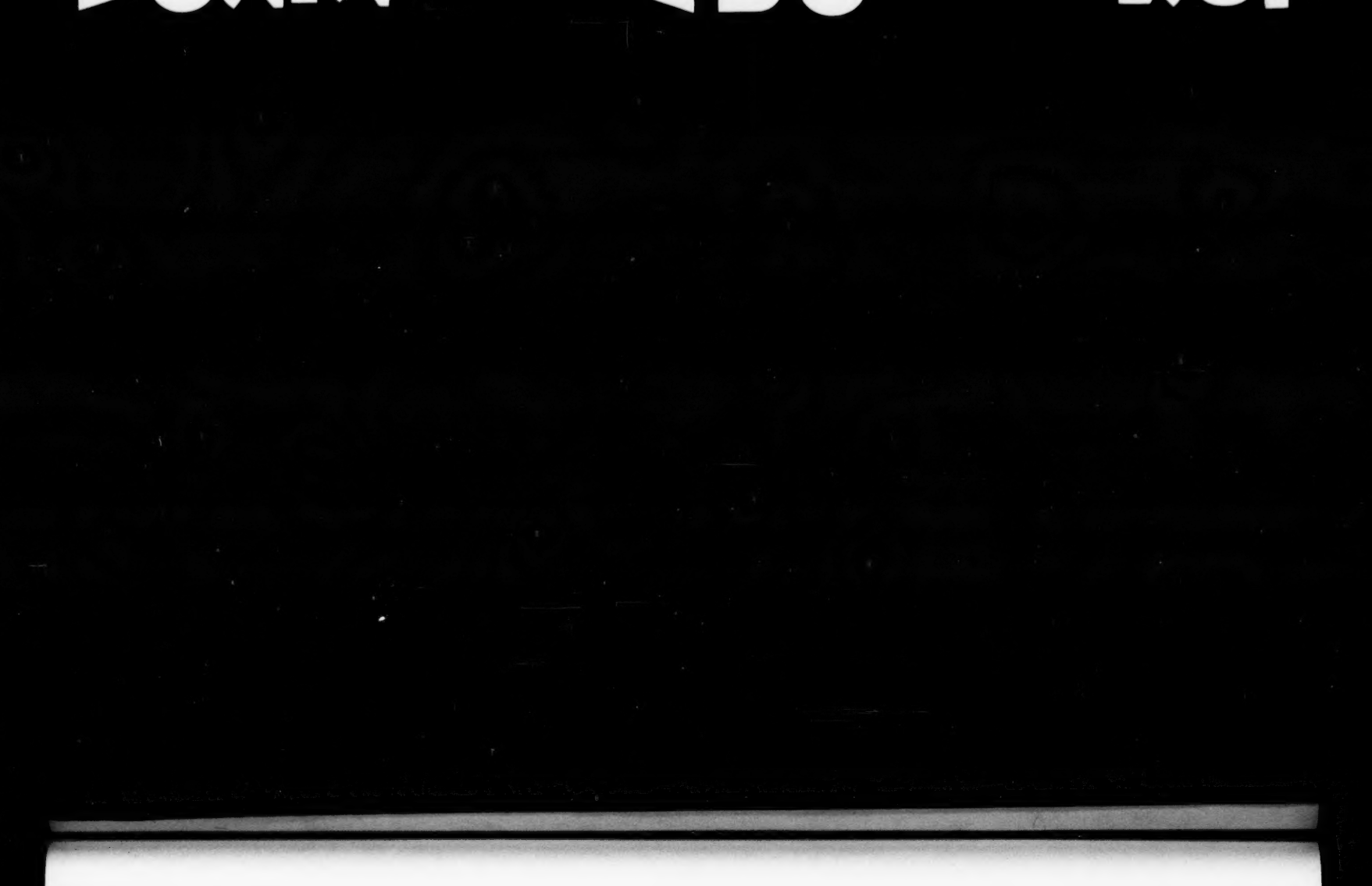
The Wassermann reaction of the blood was negative. A blood count showed 12.3 Gm. of hemoglobin and 5,700 white blood cells, with a normal differential count. The erythrocyte sedimentation rate was 12 mm. per hour. Biopsy of a specimen from a vulvar lesion, performed because of pruritus, showed leukoplakia. A roentgenogram of the chest revealed a mediastinal hernia. The results of urinalysis were normal. The urea nitrogen was 13 mg. per hundred cubic centimeters. A patch test with 10 per cent nickel sulfate gave positive reactions on one occasion.

Since discharge from the hospital in April 1948 the patient has been followed in the outpatient department and has been studied by the medical, orthopedic, nose and throat, ophthalmologic and psychiatric services. At the nose and throat service it was believed that the patient might have pemphigus because of the lesions on the tongue, gums, tonsillar pillars, epiglottis and larynx.

Since Nov. 1, 1948, the patient has been taking carbarsone, 250 mg. daily for three days followed by a three day rest, and also therapeutic doses of vitamin A, the B complex and ascorbic acid, with no effect on the lesions of the mucous membranes.

DISCUSSION

DR. HELEN O. CURTH: I can of course judge the lesions only as they are today. They are small, sharply but irregularly circumscribed aphthous lesions of the lip, gums and tongue. Such lesions may also occur on the pharynx, larynx and esophagus. The fact that the woman has not lost any weight would also speak against pemphigus vulgaris. I could not detect any other classic manifestations of Behcet's disease. However, the patient may have some form of arthritis. I should recommend that she be put on a restrictive diet, avoiding foods which may cause aphthous oral lesions. She should also avoid brushing her teeth, because these ulcerations follow frequent trauma.

We may have to wait and see whether she acquires additional signs, such as erythema nodosum or unspecific hypersensitivity to injections, which would speak in favor of Behcet's syndrome. Biopsy may help to differentiate the condition from pemphigus because the histologic picture in Behcet's syndrome is fairly characteristic and would show vasculitis or thrombosis of the deep vessels.

Ichthyosis Mitis. Presented by DR. SAMUEL M. PECK.
Steatocystoma Multiplex. Presented by DR. SAMUEL M. PECK.
Sensitivity to Everon.® Presented by DR. SAMUEL M. PECK.
Sjögren's Syndrome. Presented by DR. HOWARD T. BEHRMAN. (Previously presented one year before.)
Lichen Planopilaris. Presented by DR. HOWARD T. BEHRMAN.
Scleroderma (Acrosclerosis). Presented by DR. SAMUEL M. PECK.
Macular Atrophy in Association with Acrodermatitis Chronica Atrophicans. Presented by DR. SAMUEL M. PECK.